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(71) Applicant *(for all designated States except US)*: **METHYLGENE INC.** [CA/CA]; 7220 Frederick-Banting, St-Laurent, Québec H4S 2A1 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DELORME, Daniel** [CA/CA]; 7170 Frederick-Banting, #200, St-Laurent, Quebec H4S 2A1 (CA). **VAISBURG, Arkadii** [CA/CA]; #10 Riverwood Grove, Kirkwood, Quebec H9J 2X2 (CA). **MORADEI, Oscar** [AR/CA]; 27 Rolland-Laniel, Kirkland, Quebec H9J 4A5 (CA). **LEIT, Silvana** [AR/CA]; 27 Rolland-Laniel, Kirkland, Quebec H9J 4A5 (CA). **RAEPPEL, Stephane** [FR/CA]; 5041 Laurin, Pierrefonds, Quebec H8Y 3R4 (CA). **FRECHETTE, Sylvie** [CA/CA]; 2380 Duff Court, #8, Montreal, Quebec H8S 1G2 (CA). **BOUCHAIN, Giliane** [CA/CA]; 15 Hidden Forest Drive, Cedar Valley, Ontario L0G 1E0 (CA). **ZHOU, Zhihong** [CA/CA]; 104 Kirkland Boulevard, Kirkland, Québec H9J 1N9 (CA). **PAQUIN, Isabelle** [CA/CA]; 2250 Keller, Saint-Laurent, Québec H4K 2P9 (CA). **GAUDETTE, Frederic** [CA/CA]; 7044 Notre Dame, Ste-Dorothée, Quebec H7X 3Y5 (CA). **ISAKOVIC, Ljubomir** [CA/CA]; 1850 Lincoln Avenue, Apt. 802, Montreal, Quebec H3H 1H4 (CA).

(74) Agent: **MBM & CO.**; P.O. Box 809, Station B, Ottawa, Ontario K1P 5P9 (CA).

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(54) **Title:** INHIBITORS OF HISTONE DEACETYLASE

(57) **Abstract:** The invention relates to a series of compounds useful for inhibiting histone deacetylase (HDAC) enzymatic activity. The invention also provides a method for inhibiting histone descetylase in a cell using said compounds as well as a method for treating cell proliferative diseases and conditions using said HDAC inhibitors. Further, the invention provides pharmaceutical compositions comprising the HDAC inhibiting compounds and a pharmaceutically acceptable carrier.

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INHIBITORS OF HISTONE DEACETYLASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Application Serial No. 60/556,828, filed March 26, 2004, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] This invention relates to the inhibition of histone deacetylase. More particularly, the invention relates to compounds and methods for inhibiting histone deacetylase enzymatic activity.

Summary of the Related Art

[0003] In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

[0004] Csordas, *Biochem. J.*, **286**: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of the ε-amino groups of *N*-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton *et al.*, *Science*, **272**: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton *et al.* further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

[0005] Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). The molecular cloning of gene sequences encoding proteins with HDAC activity has established the existence of a set of discrete HDAC enzyme isoforms. Grozinger *et al.*, *Proc. Natl. Acad. Sci. USA*, **96**: 4868-4873 (1999), teaches that HDACs is divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger *et al.* also teaches that the human HDAC1, HDAC2, and HDAC3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC4, HDAC5, and HDAC6, which are members of the

second class of HDACs. Kao *et al.*, *Genes & Dev.*, **14**: 55-66 (2000), discloses HDAC7, a new member of the second class of HDACs. Van den Wyngaert, *FEBS*, **478**: 77-83 (2000) discloses HDAC8, a new member of the first class of HDACs. Zhou,X. et al., *Proc. Natl. Acad. Sci. U.S.A.* **98** (19), 10572-10577 (2001) discloses cloning and characterization of HDAC9. Kao,H.Y. et al., *J. Biol. Chem.* **277** (1), 187-193 (2002) discloses isolation and characterization of mammalian HDAC10. Gao L. et al., *J Biol Chem.* **277**(28): 25748-55 (2002) discloses cloning and functional characterization of HDAC11.

[0006] Richon *et al.*, *Proc. Natl. Acad. Sci. USA*, **95**: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from *Streptomyces hygroscopicus*, and by a synthetic compound, suberoylanilide hydroxamic acid (SAHA). Yoshida and Beppu, *Exper. Cell Res.*, **177**: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G_1 and G_2 phases of the cell cycle, implicating HDAC in cell cycle regulation. Indeed, Finnin *et al.*, *Nature*, **401**: 188-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice. Suzuki *et al.*, U.S. Pat. No. 6,174,905, EP 0847992, JP 258863/96, and Japanese Application No. 10138957, disclose benzamide derivatives that induce cell differentiation and inhibit HDAC. Delorme *et al.*, WO 01/38322 and PCT IB01/00683, disclose additional compounds that serve as HDAC inhibitors.

[0007] These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great therapeutic potential in the treatment of cell proliferative diseases or conditions. To date, few inhibitors of histone deacetylase are known in the art. There is thus a need to identify additional HDAC inhibitors and to identify the structural features required for potent HDAC inhibitory activity.

BRIEF SUMMARY OF THE INVENTION

[0008] The invention provides compounds and methods for treating cell proliferative diseases. The invention provides new inhibitors of histone deacetylase enzymatic activity.

[0009] In a first aspect, the invention provides compounds that are useful as inhibitors of histone deacetylase.

[0010] In a second aspect, the invention provides a composition comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent.

[0011] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase of the invention.

[0012] In a fourth aspect, the invention provides a method for treating cell proliferative diseases.

[0013] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0014] The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

[0015] For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

[0016] As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the ε-amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10, and HDAC-11. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

[0017] The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" are used to identify a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity. "Inhibiting histone deacetylase enzymatic activity" means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about

90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%.

[0018] Preferably, such inhibition is specific, i.e., the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

[0019] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (*e.g.* CH_3-CH_2-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-.

[0020] The term "hydrocarbyl" refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A "C_0" hydrocarbyl is used to refer to a covalent bond. Thus, "C_0-C_3-hydrocarbyl" includes a covalent bond, methyl, ethyl, ethenyl, ethynyl, propyl, propenyl, propynyl, and cyclopropyl.

[0021] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A "C_0" alkyl (as in "C_0-C_3-alkyl") is a covalent bond (like "C_0" hydrocarbyl).

[0022] The term "alkenyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon

atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0023] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0024] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0025] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0026] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, and N.

[0027] An "aryl" group is a C_6-C_{14} aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C_6-C_{10} aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C_1-C_6)alk(C_6-C_{10})aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0028] A "heterocyclic" group (or "heterocyclyl) is an optionally substituted non-aromatic mono-, bi-, or tricyclic structure having from about 3 to about 14 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. One ring of a bicyclic heterocycle or two rings of a tricyclic heterocycle may be aromatic, as in indan and 9,10-dihydro anthracene. The heterocyclic group is optionally substituted on carbon with oxo or with one of the substituents

listed above. The heterocyclic group may also independently be substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds where an annular O or S atom is adjacent to another O or S atom.

[0029] As used herein, the term “heteroaryl” refers to optionally substituted groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 pi electrons shared in a cyclic array; and having, in addition to carbon atoms, between one or more heteroatoms selected from the group consisting of N, O, and S. For example, a heteroaryl group may be pyrimidinyl, pyridinyl, benzimidazolyl, thienyl, benzothiazolyl, benzofuranyl and indolinyl. Preferred heteroaryl groups include, without limitation, thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, triazolyl, and isoxazolyl.

[0030] A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which is independently optionally substituted or unsubstituted. Preferred heteroalkyl groups comprise a C_1-C_6 alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms. Examples of preferred heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, and thiazolylethyl.

[0031] An “arylene,” “heteroarylene,” or “heterocyclylene” group is an aryl, heteroaryl, or heterocyclyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0032] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl,

isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0033] As employed herein, when a moiety (*e.g.*, cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (*e.g.*, an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, haloalkoxy, aryloxy, heteroaryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, sulfonamido, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, alkylthio, ureido, and ureidoalkyl groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

[0034] (a) halo, cyano, oxo, alkyl, alkoxy, alkylthio, haloalkoxy, aminoalkyl, aminoalkoxy, carboxy, formyl, nitro, amino, amidino, carbamoyl, guanidino, C_3-C_7 heterocycle, heterocyclylalkyl, heterocyclylcarbonyl, hydroxyalkyl, alkoxyalkyl,

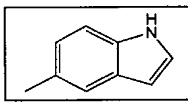
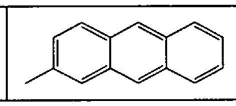
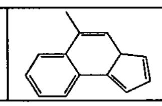
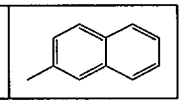
[0035] (b) C_1-C_5 alkyl or alkenyl or arylalkyl imino, carbamoyl, carbamate, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, C_2-C_8 acyl, C_2-C_8 acylamino, C_1-C_8 alkylthio, arylalkylthio, arylthio, heteroarylthio, C_1-C_8 alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0-C_6 *N*-alkyl carbamoyl, C_2-C_{15} *N,N*-dialkylcarbamoyl, C_3-C_7 cycloalkyl, aroyl, aryloxy, heteroaryloxy, arylalkyl ether, C_3-C_7 heterocyclylalkylether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3-C_7 heterocycle, heteroaryl, arylcarbamoyl, or any of these rings fused or spiro-

fused to a cycloalkyl, heterocyclyl, or aryl, wherein any of the foregoing which are additionally substitutable is further optionally substituted with one more moieties listed in (a), above; and

[0036] (c) -$(CH_2)_s$-$NR^{30}R^{31}$, wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R^{30} and R^{31} are each independently hydrogen, cyano, oxo, carboxamido, amidino, C_1-C_8 hydroxyalkyl, C_1-C_3 alkylaryl, aryl-C_1-C_3 alkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, aryl-C_1-C_3 alkoxycarbonyl, C_2-C_8 acyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

[0037] R^{30} and R^{31} taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

[0038] In addition, substituents on cyclic moieties (i.e., cycloalkyl, heterocyclyl, aryl, heteroaryl) include 5-6 membered mono- and 9-14 membered bi-cyclic moieties fused to the parent cyclic moiety to form a bi- or tri-cyclic fused ring system. For example, an optionally substituted phenyl includes, but not limited to, the following:

[0039] Preferred substituents on cyclic moieties (i.e., cycloalkyl, heterocyclyl, aryl, heteroaryl) also include groups of the formula $-K^1$-N(H)(R^{10}), wherein

[0040] K^1 is a chemical bond or C_1-C_4 alkylene;

[0041] R^{10} is selected from the group consisting of Z' and -Ak^2-Z', wherein

[0042] Ak^2 is C_1-C_4 alkylene; and

[0043] Z' is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings.

[0044] Particularly preferred substituents on cyclic moieties (such as aryl, heteroaryl, cycloalkyl, heterocyclyl, or any of these rings fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings), include 1, 2, or 3 groups independently selected from the following:

[0045] a) alkoxy, cyano, amino, oxo, haloalkyl, halo, alkyl, R_{50}-C(O)-N(R_{32})-, R_{50}-O-C(O)-N(R_{32})-, R_{50}-NH-C(O)-N(R_{32})-, R_{50}-NH-C(O)-O-, (R_{32})(R_{33})N-alkyl-, (R_{32})(R_{33})N-alkyl-O-, (R_{32})(R_{33})N-alkenylene-N(R_{32})-, N(R_{32})-aryl-N(R_{32})-C(O)-aryl-alkyl-N(R_{32})-;

[0046] wherein R_{50} is cycloakyl, heterocyclyl-C_1-C_6 alkyl-, $R_{32}R_{33}$N-alkyl-, or alkyl;

[0047] b) aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-, cycloalkyl-C_0-C_6 alkyl-, heterocyclyl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-N(R_{32})-, aryl-C(O)-, heteroaryl-C_0-C_6 alkyl-N(R_{32})-, heterocyclyl-C_0-C_6 alkyl-N(R_{32})-, aryl-O-, heteroaryl-O-, aryl-S-, heteroaryl-S-, aryl-SO_2-, heteroaryl-SO_2, aryl-C(O)N(R_{32})-, heteroaryl-C(O)N(R_{32})-, heteroaryl-C(H)(SO_2-heteroaryl)-N(R_{32})-;

[0048] wherein R_{32} and R_{33} are independently H or C_1-C_6 alkyl, or R_{32} and R_{33} taken together with the N to which they are attached form a heterocyclyl or heteroaryl;

[0049] and wherein any of the rings described in paragraphs [0045]-[0048] are further optionally substituted with 1, 2, or 3 groups independently selected from alkyl, alkoxy, thioalkoxy, alkyl-SO_2-, amino, halo, cyano, haloalkyl, hydroxyalkyl, alkoxyalkoxyalkyl, COOH, alkanoyl, alkanoate, NO_2, hydroxy, haloalkoxy, (R_{32})(R_{33})N–C_0-C_6 alkyl-, (R_{32})(R_{33})N–C_0-C_6 alkyl-O-, (R_{32})(R_{33})N–C(O)-, heteroaryl, alkyl-C(O)N(R_{32})-, aryl-O-, (R_{32})(R_{33})N–SO_2-, aryl, and (R_{32})(R_{33})N–alkyl-C(O)N(R_{32})-.

[0050] A “halohydrocarbyl” is a hydrocarbyl moiety in which from one to all hydrogens have been replaced with one or more halo.

[0051] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (*i.e.*, R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (*i.e.*, NH_2-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally optionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH_2, alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0052] The term “radical” as used herein means a chemical moiety comprising one or more unpaired electrons.

[0053] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluoro-3-propylphenyl. As another non-limiting example, substituted *N*-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-

cyclopentyl-octyl. Included within this definition are methylenes ($-CH_2-$) substituted with oxygen to form carbonyl -CO-).

[0054] An "unsubstituted" moiety as defined above (*e.g.*, unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

[0055] Throughout the specification preferred embodiments of one or more chemical substituents are identified. Also preferred are combinations of preferred embodiments. For example, paragraph [0080] describes preferred embodiments of Cy in the compound of formula (1a) and paragraph [0079] describes preferred embodiments of W of the compound of formula (1a). Thus, also contemplated as within the scope of the invention are compounds of formula (1) in which Cy is as described in paragraph [0080] and W is as described in paragraph [0079].

[0056] Some compounds of the invention may have chiral centers and/or geometric isomeric centers (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers. The invention also comprises all tautomeric forms of the compounds disclosed herein. Where compounds of the invention include chiral centers, the invention encompasses the enantiomerically pure isomers of such compounds, the enantiomerically enriched mixtures of such compounds, and the racemic mixtures of such compounds.

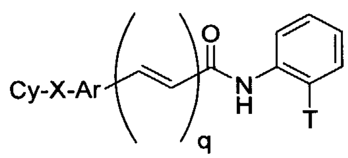
[0057] The compounds of the invention may be administered in the form of an *in vivo* hydrolyzable ester or *in vivo* hydrolyzable amide. An *in vivo* hydrolyzable ester of a compound of the invention containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolyzed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}-alkoxymethyl esters (*e.g.*, methoxymethyl), C_{1-6}-alkanoyloxymethyl esters (*e.g.*, for example pivaloyloxymethyl), phthalidyl esters, C_{3-8}-cycloalkoxycarbonyloxyC_{1-6}-alkyl esters (*e.g.*, 1-cyclohexylcarbonyloxyethyl); 1,3-dioxolen-2-onylmethyl esters (*e.g.*, 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}-alkoxycarbonyloxyethyl esters (*e.g.*, 1-methoxycarbonyloxyethyl) and may be formed at any carboxy group in the compounds of this invention.

[0058] An *in vivo* hydrolyzable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters and a-acyloxyalkyl ethers and related compounds which as a result of the in vivo hydrolysis of the ester breakdown to give the parent

hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in vivo hydrolyzable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(*N,N*-dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), *N,N*-dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring. A suitable value for an *in vivo* hydrolyzable amide of a compound of the invention containing a carboxy group is, for example, a *N*-C_{1-6}-alkyl or N,N-di-C_{1-6}-alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

Compounds

[0059] In a first aspect, the invention provides novel inhibitors of histone deacetylase. In a first embodiment, the novel inhibitors of histone deacetylase are represented by formula (1):



(1)

[0060] and pharmaceutically acceptable salts thereof, wherein

[0061] X is selected from the group consisting of a chemical bond, L, W-L, L-W, L-W-L, and L-W'-L-W', wherein

[0062] Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

[0063] W, at each occurrence, is S, O, C=O, -NH-C(=O)-NH-, -$NHSO_2$-, or N(R^9), where R^9 is selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and t-butoxycarbonyl;

[0064] W' at each occurrence is independently a chemical bond, S, O, or NH; and

[0065] L, at each occurrence, is independently a chemical bond or C_1-C_4 alkylene; or

[0066] Ar is arylene or heteroarylene, each of which is optionally substituted;

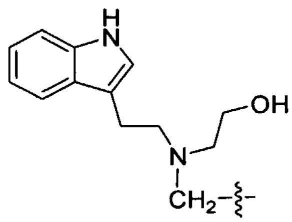
[0067] q is 0 or 1; and

[0068] T is NH_2 or OH;

[0069] provided that when Cy is naphthyl, X is $-CH_2-$, Ar is phenyl, and q is 0 or 1, T is not OH.

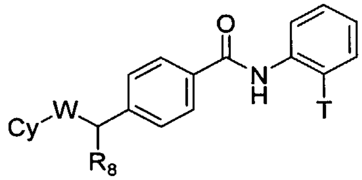
[0070] In some preferred embodiments of the compound according to paragraph [0059], q is 1, and T is NH_2.

[0071] Preferred compounds of the embodiments of paragraph [0070] include those wherein Ar is phenylene, and Cy-X- is



[0072] In some preferred embodiments of the compounds according to paragraph [0059], q is 0.

[0073] In a preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0072] having formula (1a):



(1a)

[0074] and pharmaceutically acceptable salts thereof, wherein

[0075] Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

[0076] W is S, O, or $N(R_9)$, wherein R_9 is hydrogen or C_1-C_6-alkyl;

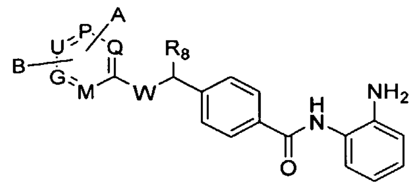
[0077] R_8 is H or C_1-C_4 alkyl; and

[0078] T is NH_2 or OH.

[0079] In some preferred embodiments of the compounds according to paragraph [0073], W is NH or S.

[0080] Preferred compounds according to the invention, and particularly paragraph [0079], include those wherein Cy is selected from phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiazolyl, benzothiazolyl, benzoimidazolyl, and benzotriazolyl, each of which is optionally substituted.

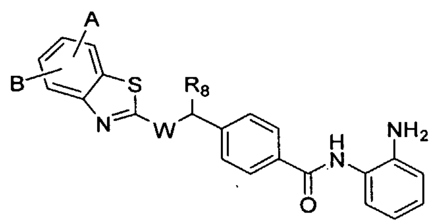
[0081] Preferred compounds according to paragraph [0080] include those of the structure 1a-1:



1a-1

[0082] and pharmaceutically acceptable salts thereof, wherein W is NH or S; P, Q, M, G and U are independently CH or N, provided that no more than two of P, Q, M, G and U are N and in the ring containing P, Q, M, G, and U, an annular S or O is not adjacent to another annular S or O; R_8 is H or C_1-C_4 alkyl; and A and B are as defined below.

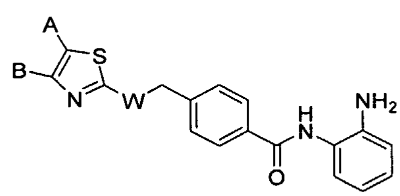
[0083] Preferred compounds according to paragraph [0080] include those of the structure 1a-2:



1a-2

[0084] and pharmaceutically acceptable salts thereof, wherein W is S or NH; R_8 is H or C_1-C_4 alkyl; and A and B are as defined below.

[0085] Preferred compounds according to paragraph [0080] include those of the structure 1a-3:

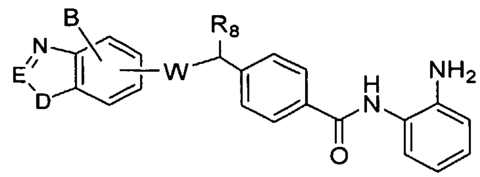


1a-3

[0086] and pharmaceutically acceptable salts thereof, wherein W is S or NH, and A and B are as defined below.

[0087] Preferred compounds according to paragraph [0085] include those wherein W is NH.

[0088] Preferred compounds according to paragraph [0080] include those of the structure 1a-4:

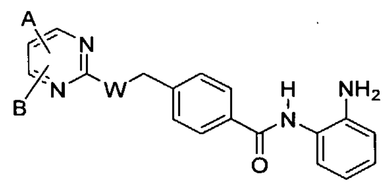


1a-4

[0089] and pharmaceutically acceptable salts thereof, wherein W is S or NH; D is N-R_{10} or S, E is N or C-A; R_8 and R_{10} are independently H or C_1-C_4 alkyl; and A and B are as described below.

[0090] Preferred compounds according to paragraph [0088] include those wherein W is NH.

[0091] Preferred compounds according to paragraph [0081] include those of the formula 1a-5:



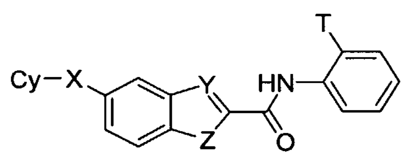
1a-5

[0092] and pharmaceutically acceptable salts thereof.

[0093] Preferred compounds according to paragraph [0091] include those wherein W is NH.

[0094] Preferred compounds according to paragraphs [0073] and [0079] also include those wherein W is NH and Cy is quinoxalinyl, phthalimidyl, or benzodioxolyl, each of which is optionally substituted with A and/or B, wherein A and B are as defined below.

[0095] In a further preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0059] having formula (1b):



(1b)

[0096] and pharmaceutically acceptable salts thereof, wherein

[0097] Cy is aryl, heteroaryl, cycloalkyl or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

[0098] X is L, W-L, or L-W, wherein

[0099] W, at each occurrence, is S, O, or NH; and

[0100] L is -CH_2-;

[0101] Y is N or CH;

[0102] Z is O, S, NR_{12} or CH_2;

[0103] R_{12} is H or C_1-C_4 alkyl; and

[0104] T is NH_2 or OH.

[0105] In some preferred embodiments of the compounds according to paragraph [0095], T is NH_2.

Preferred compounds according to each of paragraphs [0095] and [0105] include those wherein X is -S-CH_2-, -NH-CH_2- or -CH_2-NH-.

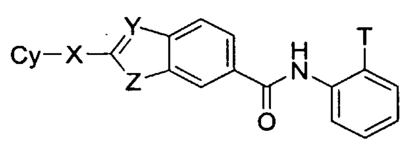
Preferred compounds according to paragraphs [0095], [0105], and 0 include those wherein Cy is aryl or heteroaryl, each of which is optionally substituted.

[0106] Preferred compounds according to each of paragraphs [0095]-0 include those wherein Cy is phenyl, pyridyl, pyrimidinyl, or benzothiazolyl, each of which is optionally substituted.

[0107] Preferred compounds according to each of paragraphs [0095]-[0106] include those wherein Cy is substituted with A and/or B, wherein A and B are as defined in paragraph [0185].

[0108] Preferred compounds according to paragraph each of paragraphs [0095]-[0106] include those wherein Cy is optionally substituted with one two or three groups independently selected from alkoxy, acyl, morpholino, or phenyl optionally substituted with alkoxy.

[0109] In a further preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0059] having formula (1c):



(1c)

[0110] and pharmaceutically acceptable salts thereof, wherein

[0111] Cy is aryl, heteroaryl, cycloalkyl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

[0112] X is L, W-L, or L-W, wherein

[0113] W, at each occurrence, is S, O, or NH; and

[0114] L is -CH_2-;

[0115] Y is N or CH;

[0116] Z is O, S, NR_{12} or CH_2;

[0117] R_{12} is H or C_1-C_4 alkyl; and

[0118] T is NH_2 or OH.

[0119] In some preferred embodiments of the compounds according to paragraph [0109], T is NH_2.

[0120] Preferred compounds according to each of paragraphs [0109]-[0119] include those wherein X is -S-CH_2-, -NH-CH_2- or -CH_2-NH-.

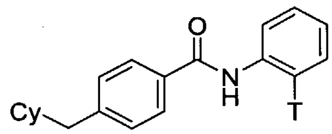
[0121] Preferred compounds according to each of paragraphs [0109]-[0120] include those wherein Cy is aryl or heteroaryl, each of which is optionally substituted.

[0122] Preferred compounds according to each of paragraphs [0109]-[0121] include those wherein Cy is phenyl, pyridyl, pyrimidinyl, or benzothiazolyl, each of which is optionally substituted.

[0123] Preferred compounds according to each of paragraphs [0109]-[0122] include those wherein Cy is substituted with A and/or B, wherein A and B are as defined in paragraph [0185].

[0124] Preferred compounds according to each of paragraphs [0109]-[0122] include those wherein Cy is optionally substituted with one two or three groups independently selected from alkoxy, haloalkoxy, acyl, morpholino, or phenyl optionally substituted with alkoxy.

[0125] In a further preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0059] having formula (1d):



(1d)

[0126] and pharmaceutically acceptable salts thereof, wherein

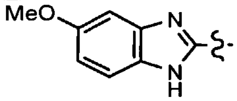
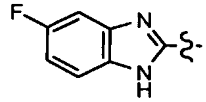
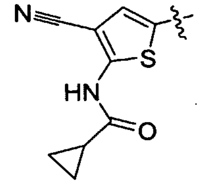
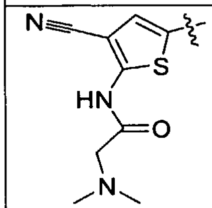
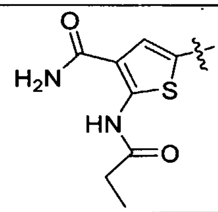
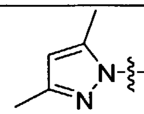
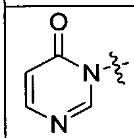
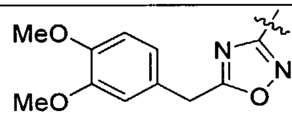
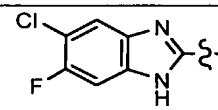
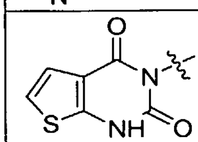
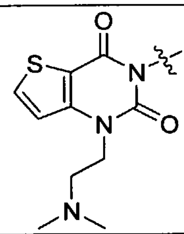
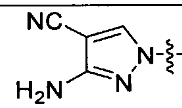
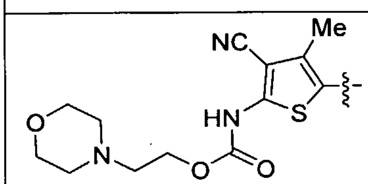
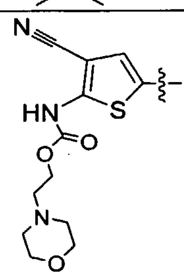
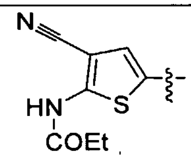
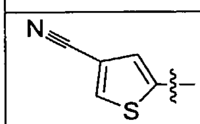
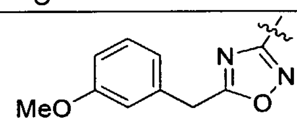
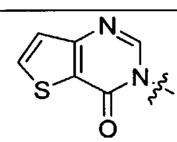
[0127] Cy is aryl, or heteroaryl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted; and

[0128] T is NH_2 or OH.

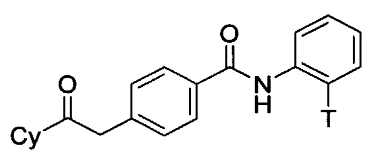
[0129] In some preferred embodiments of the compounds according to paragraph [0125], T is NH_2.

[0130] Preferred compounds according to each of paragraphs [0125]-[0129] include those wherein Cy is optionally substituted heteroaryl or optionally substituted heterocyclyl, each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted.

[0131] Preferred compounds according to each of paragraphs [0125]-[0130] include those wherein Cy is:

[0132] In a further preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0059] having formula (1e):



(1e)

[0133] and pharmaceutically acceptable salts thereof, wherein

[0134] Cy is aryl, heteroaryl, cycloalkyl,or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted; and

[0135] T is NH_2 or OH.

[0136] In some preferred embodiments of the compounds according to paragraph [0132], T is NH_2.

[0137] Preferred compounds according to each of paragraphs [0132]-[0136] include those wherein Cy is heterocyclyl or heteroaryl, each of which is optionally substituted, and each of which contains at least one nitrogen atom as part of the ring.

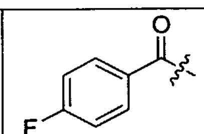
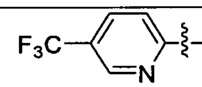
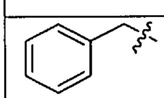
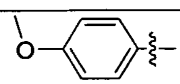
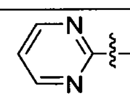
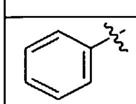
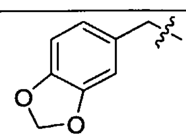
[0138] Preferred compounds according to each of paragraphs [0132]-[0137] include those wherein Cy is bound to phenyl through a nitrogen atom.

[0139] Preferred compounds according to each of paragraphs [0132]-[0137] include those wherein Cy is heterocyclyl, which is optionally substituted.

[0140] Preferred compounds according to paragraph each of paragraphs [0132]-[0137] and [0139] include those wherein Cy is piperidinyl, or piperazinyl, each of which is optionally substituted.

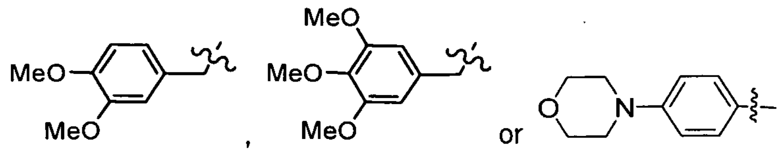
[0141] Preferred compounds according to each of paragraphs [0132]-[0140] include those wherein Cy is optionally substituted with one or two substituents independently selected from A and B, wherein A and B are as defined in paragraph [0185].

[0142] Preferred compounds according to each of paragraphs [0132]-[0140] include those wherein Cy is optionally substituted with one or two substituents independently selected from:

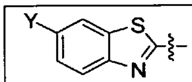
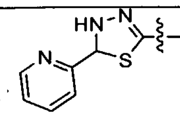
-CN,	 ,	 ,
 ,	 ,	 ,
 , and	 .	

[0143] Preferred compounds according to paragraph [0072] include those wherein Ar is phenylene, indolyl or indolinyl, each of which is optionally substituted, and X is absent, CH_2, -O-CH_2-, -S-CH_2-, -S-C(CH_3)(H)-, or -N(R_9)-CH_2-.

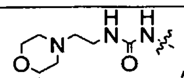
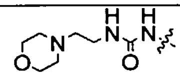
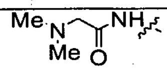
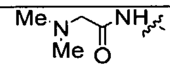
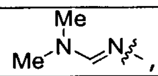
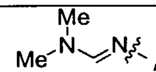
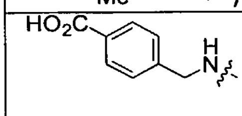
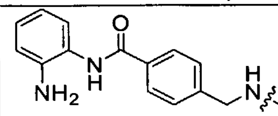
[0144] Preferred compounds according to paragraph [0143] include those wherein Ar is an indolyl or indolinyl group, X is CH_2 or $-N(R_9)-CH_2-$, and Cy is:



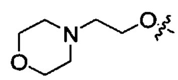
[0145] Preferred compounds according to paragraph [0143] include those wherein Ar is phenylene, X is $-S-CH_2-$, or $-S-C(CH_3)(H)-$, and Cy is:

 ,	or  ,

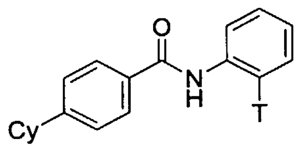
[0146] wherein Y is selected from:

 ,	 ,
 ,	 ,
 ,	 ,
 , and	 ;

[0147] Preferred compounds according to paragraph [0145] include those wherein Y' is H, and Y'' is:



[0148] Preferred compounds according to paragraph [0143] include those of the formula (1f):

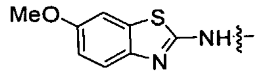


(1f).

[0149] Preferred compounds according to paragraph [0148] include those wherein Cy is heterocyclyl or heteroaryl, each of which is optionally substituted, and each of which contains at least one nitrogen atom as part of the ring.

[0150] Preferred compounds according to paragraph [0149] include those wherein Cy is bound to the phenyl through a nitrogen atom.

[0151] Preferred compounds according to paragraph [0148] include those wherein Cy is: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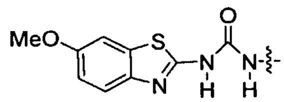
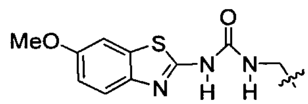

, or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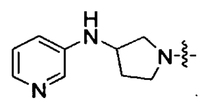
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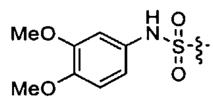
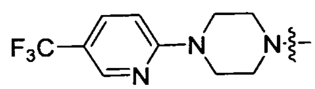
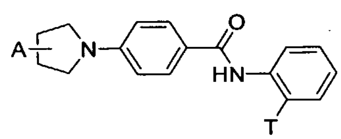

, or


.

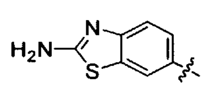
[0152] Preferred compounds according to paragraph [0148] include those of the formula (1f-1):


(1f-1)

[0153] and pharmaceutically acceptable salts thereof, wherein T is OH or NH_2 and A is as defined below.

[0154] Preferred compounds according to paragraph [0152] include those wherein T is NH_2.

[0155] Preferred compounds according to paragraph [0143] include those wherein Ar is phenylene, X is -O-CH_2-, and Cy is: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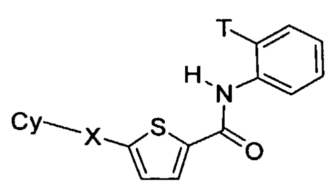
[0156] In a further preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0059] having formula (1g):


(1g)

[0157] and pharmaceutically acceptable salts thereof, wherein

[0158] Cy is aryl, or heteroaryl, cycloalkyl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

[0159] X is L, W-L, or L-W, wherein

[0160] W, at each occurrence, is S, O, or NH; and

[0161] L is $-CH_2-$;

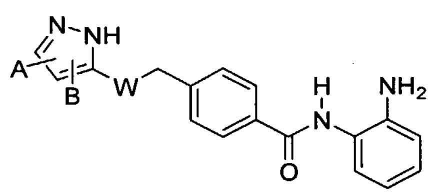
[0162] T is NH_2 or OH.

[0163] Preferred compounds according to paragraph [0156] include those wherein Cy is optionally substituted heteroaryl. More preferablly, Cy is optionally substituted pyrimidinyl. Also preferably, Cy is pyrimidinyl substituted with pyridyl.

[0164] Preferred compounds according to paragraph [0156] also include those wherein X is $-NH-CH_2-$.

[0165] Preferred compounds according to paragraph [0156] also include compounds wherein T is NH_2.

[0166] Preferred compounds according to paragraph [0059] include those of the formula (1h):



(1h)

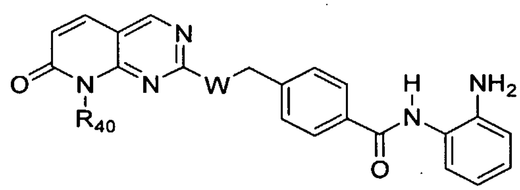
[0167] and pharmaceutically acceptable salts thereof, where W is S, O, or NH and A and B are as described below.

[0168] Preferred compounds according to paragraph [0166] include those wherein W is NH.

[0169] Preferred compounds according to paragraph [0166] include those wherein A is optionally substituted pyridyl or optionally substituted phenyl.

[0170] Preferred compounds according to paragraph [0166] include those wherein B is H or halo. Preferably, halo is chloro.

[0171] Preferred compounds according to paragraph [0059] include those of the formula (1i):


(1i)

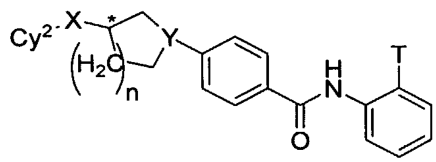
[0172] and pharmaceutically acceptable salts thereof, where W is S, O, or NH and R40 is H or C_1-C_6 alkyl.

[0173] Preferred compounds according to paragraph [0171] include those wherein W is NH.

[0174] Preferred compounds according to paragraph [0171] include those wherein R_{40} is H.

[0175] Preferred compounds according to paragraph [0171] include those wherein R_{40} is methyl.

[0176] In a further preferred embodiment, the novel histone deacetylase inhibitors of the invention are compounds of formula (2)


(2)

[0177] and pharmaceutically acceptable salts thereof, wherein

[0178] Cy^2 is aryl or heteroaryl, each of which is optionally substituted and wherein each of aryl, and heteroaryl is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

[0179] X is selected from the group consisting of: a covalent bond, C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(CO)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(NR^7)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(S)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(O)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(SO)-C_0-C_4-hydrocarbyl,

C_0-C_4-hydrocarbyl -(SO_2)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(NH)-(CO)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(CO)-(NH)-C_0-C_4-hydrocarbyl, -NH-CO-NH-, -NH-CS-NH-, -O-CO-O-, -O-CS-O-, -NH-C(NH)-NH-, -$S(O)_2$-N(R^7)-, -N(R^7)-$S(O)_2$-, -NH-C(O)-O-, and -O-C(O)-NH-,

[0180] wherein R^7 is selected from the group consisting of hydrogen, C_1-C_5-alkyl, aryl, aralkyl, acyl, heterocyclyl, heteroaryl, SO_2-alkyl, SO_2-aryl, CO-alkyl, CO-aryl, CO-NH-alkyl, CO-NH-aryl, CO-O-alkyl and CO-O-aryl, each of which is optionally substituted,

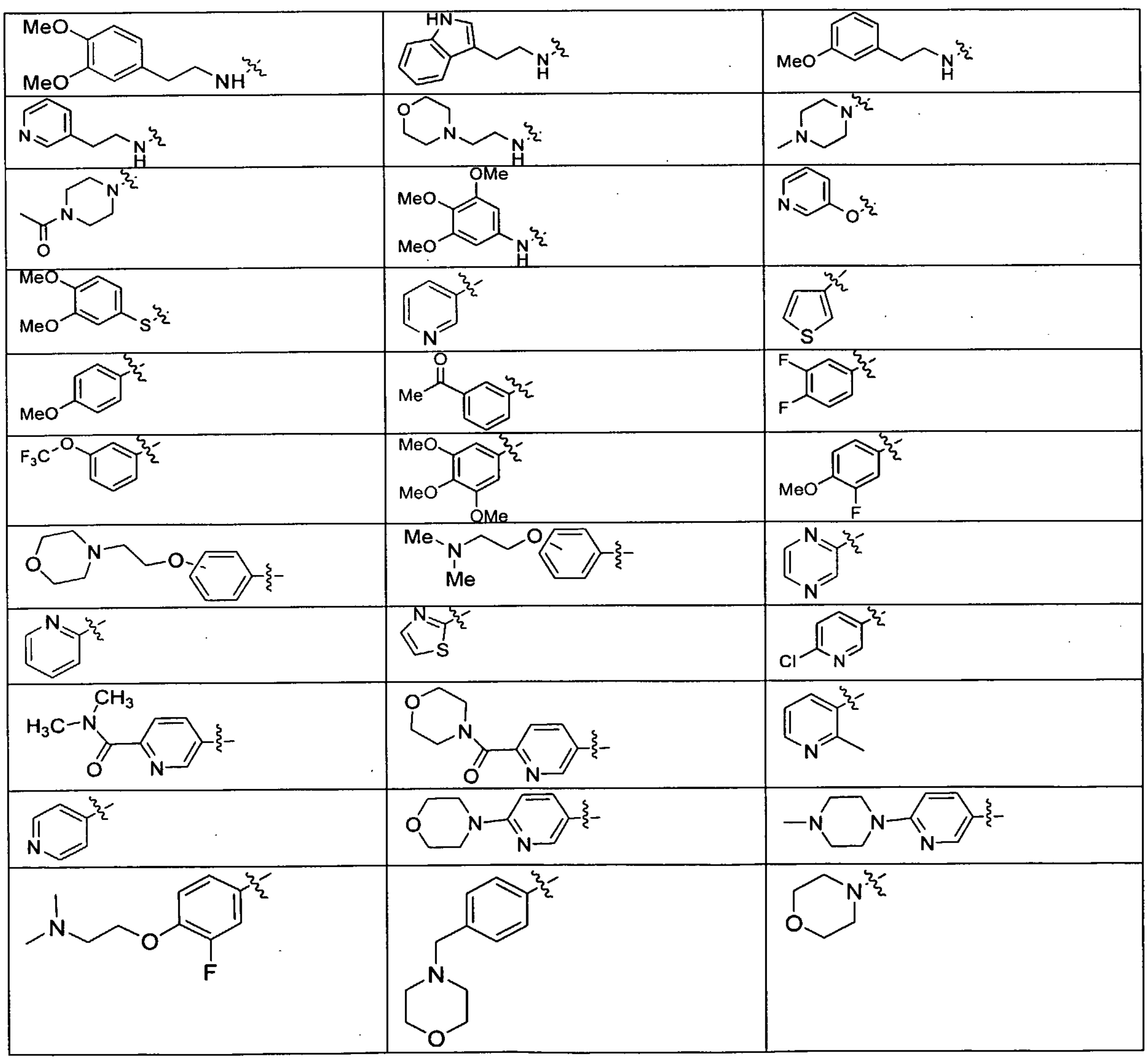
[0181] n is 0 to 4,

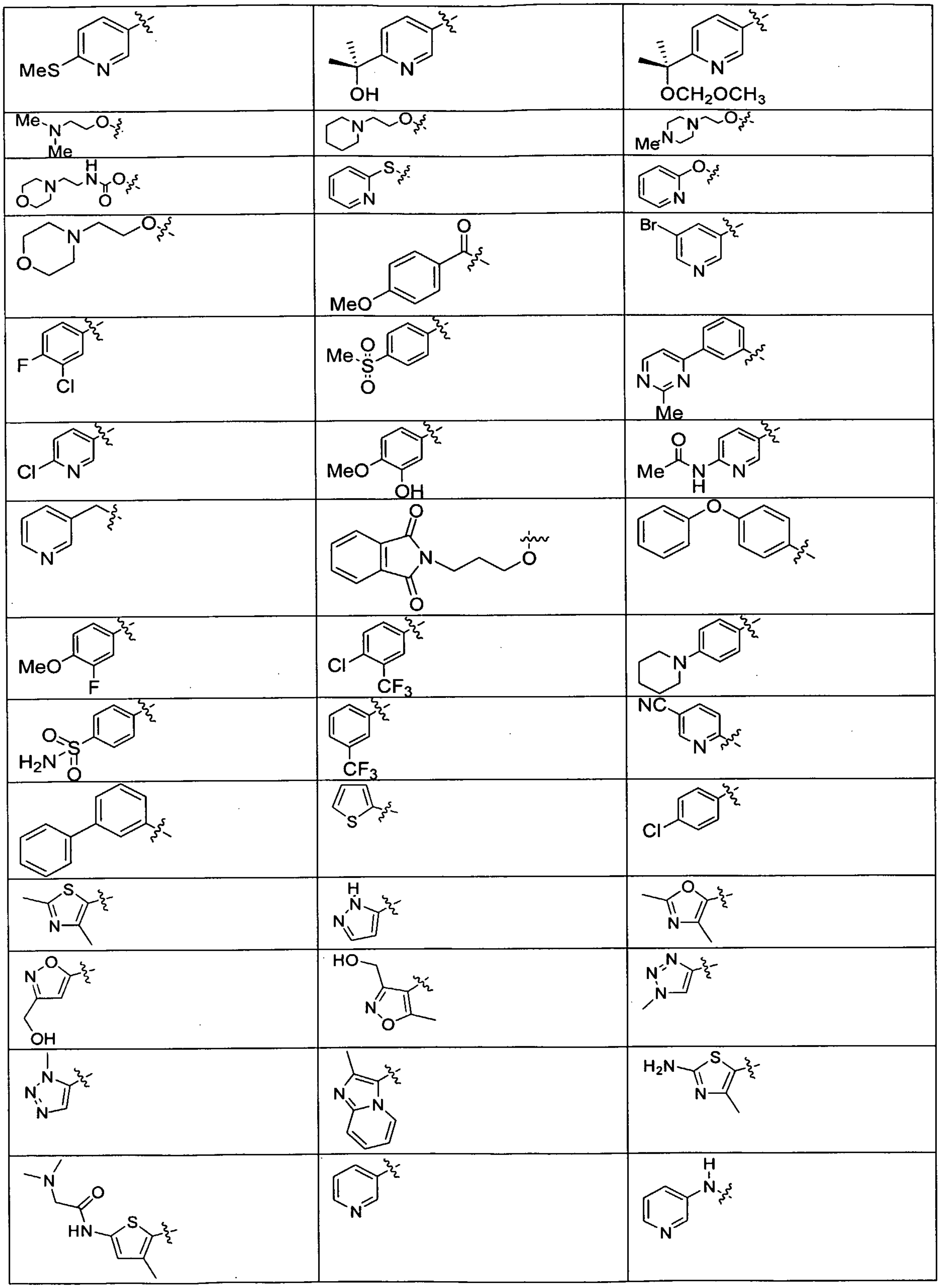
[0182] Y is N or CH,

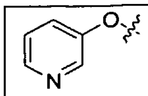
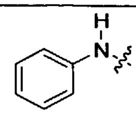
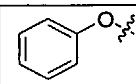
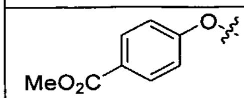
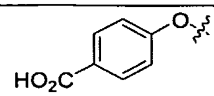
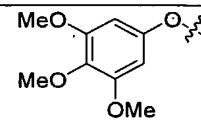
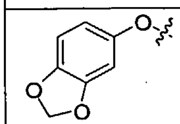
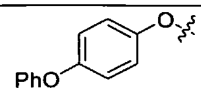
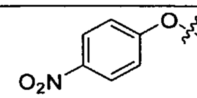
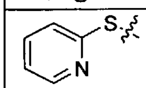
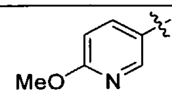
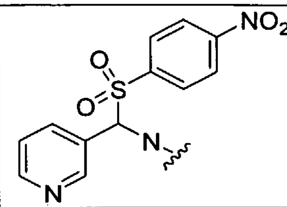
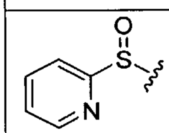
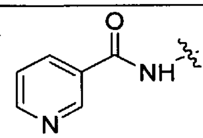
[0183] T is NH_2 or OH.

[0184] Compounds of formula (2) contain a chiral center (indicated by the asterisk (*)). The invention encompasses both racemic mixtures and enantiomerically enriched mixtures of compounds of formula (2), as well as the enantiomerically pure isomers of compounds of formula (2). Preferably in enantiomerically enriched mixtures there is greater or equal to 80% of one enantiomer, more preferably greater than 90%, 95%, or 98%.

[0185] Groups A and B are the same or different and are independently selected from H, halogen, C_1-C_4 alkyl, optionally substituted alkoxy including aminoalkoxy, haloalkoxy and heteroarylalkoxy, alkoxyalkyl, haloalkyl, amino, nitro, alkylthio, acylamino, carbamoyl, or the following:





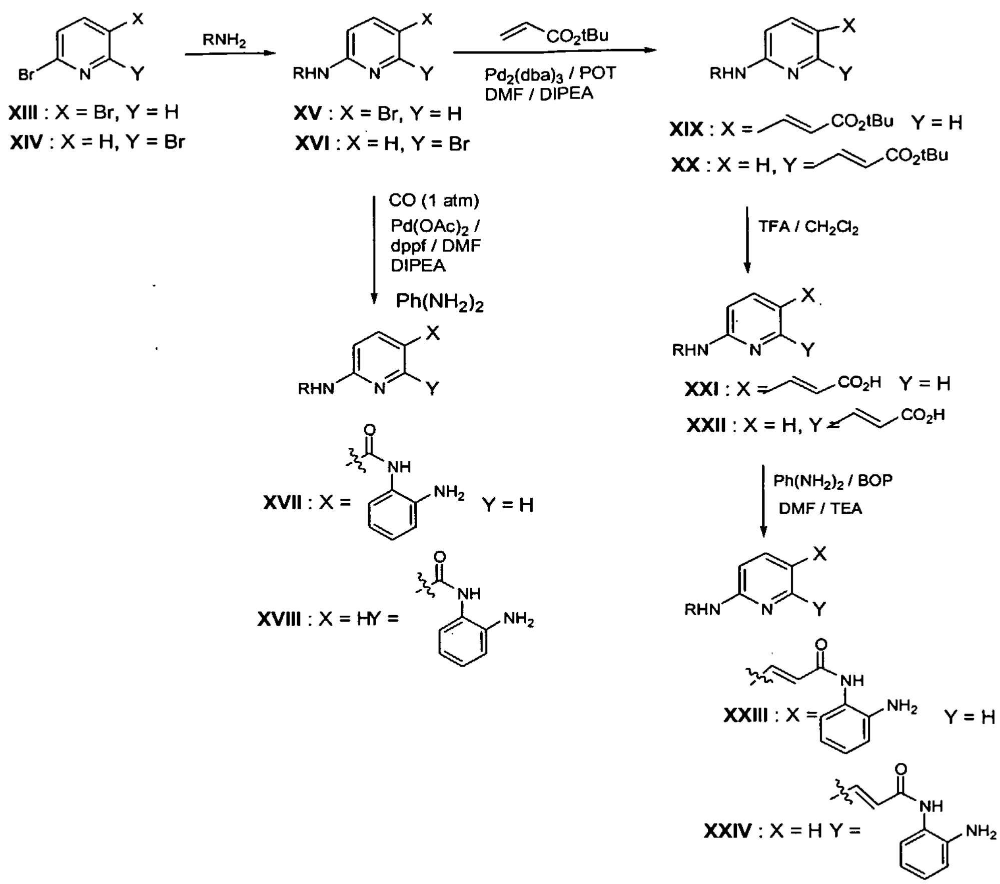
		
		
		
		
		

Synthesis

[0186] Compounds of formula (1), wherein Ar is pyridylene and X comprises -N(R^9)- preferably may be prepared according to the procedures illustrated in Scheme A. Dibromopyridine **XIII** or **XIV** is treated with amine RNH_2 to produce aminobromopyridine **XV** or **XVI**, respectively. Treatment of **XV** or **XVI** with diacetoxypalladium, diphenylphosphinoferrocene, DMF, diisopropylethylamine, and phenylenediamine under carbon monoxide yields anilinyl amide **XVII** or **XVIII**, respectively.

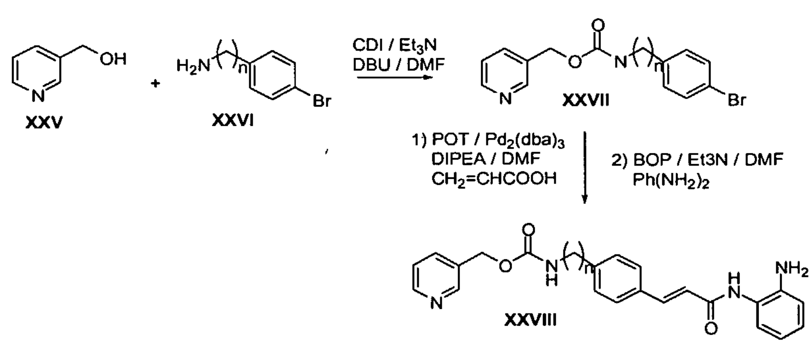
[0187] Treatment of **XV** or **XVI** with tert-butylacrylate, diisopropylethylamine, dibenzylacetone palladium, and tri-o-tolylphosphine (POT) in DMF under nitrogen affords compounds **XIX** and **XX**, respectively. The ester moiety of **XIX** or **XX** is hydrolyzed to produce the corresponding acid moiety in **XXI** or **XXII**, respectively, by reaction with trifluoroacetic acid in dichloromethane. Treatment of the acid **XXI** or **XXII** with phenylenediamine, BOP, and triethylamine affords the anilinyl amide **XXIII** or **XXIV**, respectively.

[0188] Scheme A



[0189] Compounds wherein X comprises -O-C(O)-NH- preferably may be prepared according to the synthetic route depicted in Scheme B. Thus, carbinol **XXV** is added to bromobenzylamine **XXVI** with carbonyldiimidazole (CDI), triethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF to produce compound **XXVII**. The remaining synthetic steps in the production of anilinyl amide **XXVIII** are as described above for Scheme A.

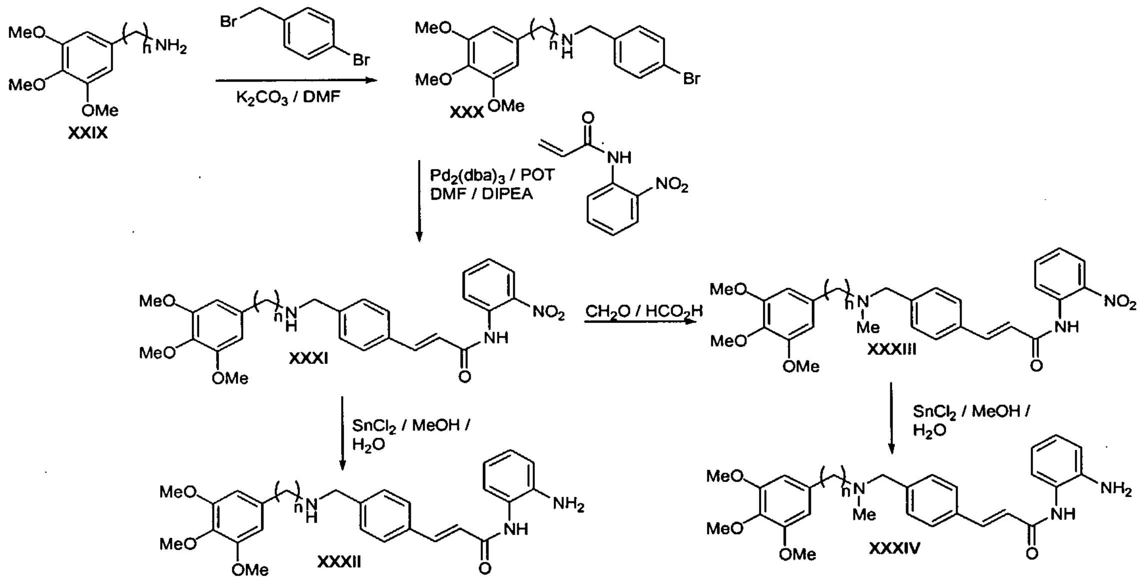
[0190] Scheme B



[0191] Compounds wherein X comprises -N(R^9)-, preferably may be prepared as outlined in Scheme C. Amine XXIX is reacted with p-bromobenzylbromide in the presence of potassium carbonate in DMF to produce bromobenzylamine XXX. Treatment of XXX with nitroacrylanilide, dibenzylacetone palladium, POT, anddiisopropylethylamine in DMF affords nitroanilide XXXI. Nitroanilide XXXI is converted to the corresponding anilinyl amide XXXII by treatment with stannous chloride in methanol and water.

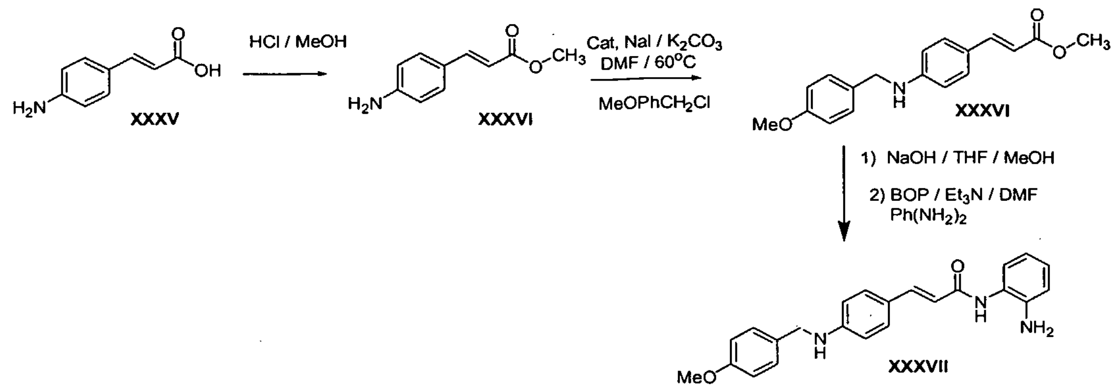
[0192] Treatment of amine **XXXI** in formic acid with paraformaldehyde provides methylamine **XXXIII**. The nitroanilide moiety in **XXXIII** is then converted to the corresponding anilinyl amide moiety in **XXXIV** by treatment with stannous chloride in methanol and water.

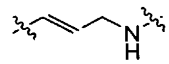
[0193] Scheme C



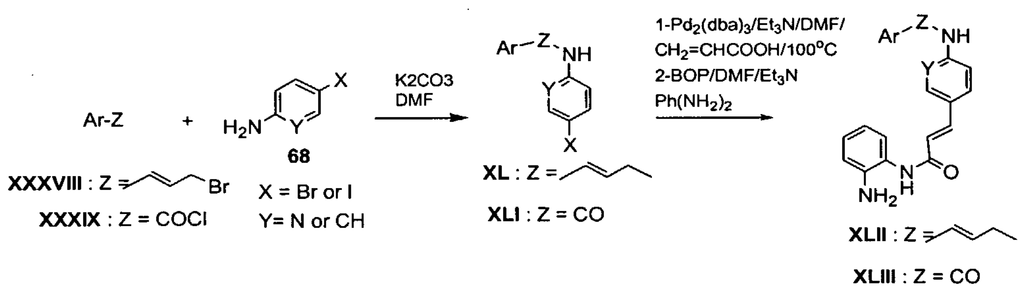
[0194] Alternatively, compounds wherein X comprises -N(R^9)- may be prepared according to the synthetic route depicted in Scheme D. Carboxylic acid **XXXV** in methanol is treated with hydrochloric acid to produce ester **XXXVI**. Conversion of the primary amine moiety in **XXXVI** to the secondary amine moiety in **XXXVI** is effected by treatment with a catalyst such as triethylamine, methoxybenzylchloride, sodium iodide, and potassium carbonate in DMF at 60 °C. Ester **XXXVI** is converted to anilinyl amide **XXXVII** by treatment with sodium hydroxide, THF, and methanol, followed by BOP, triethylamine, and phenylenediamine in DMF, as described above for Scheme A.

[0195] Scheme D



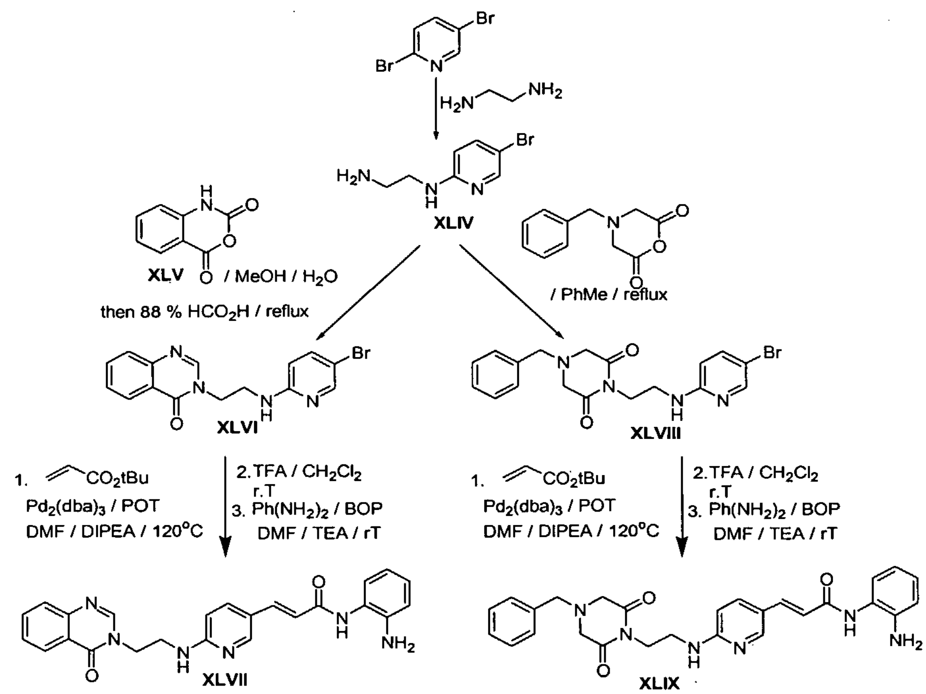
[0196] Compounds wherein X comprises  or -C(O)-NH-, preferably may be prepared according to the procedures illustrated in Scheme E. Addition of amine **68** to haloaryl compound **XXXVIII** or **XXXIX** and potassium carbonate in DMF provides arylamine **XL** or **XLI**, respectively. Anilinyl amide **XLII** or **XLIII** is then prepared using procedures analogous to those set forth in Schemes A-D above.

[0197] Scheme E



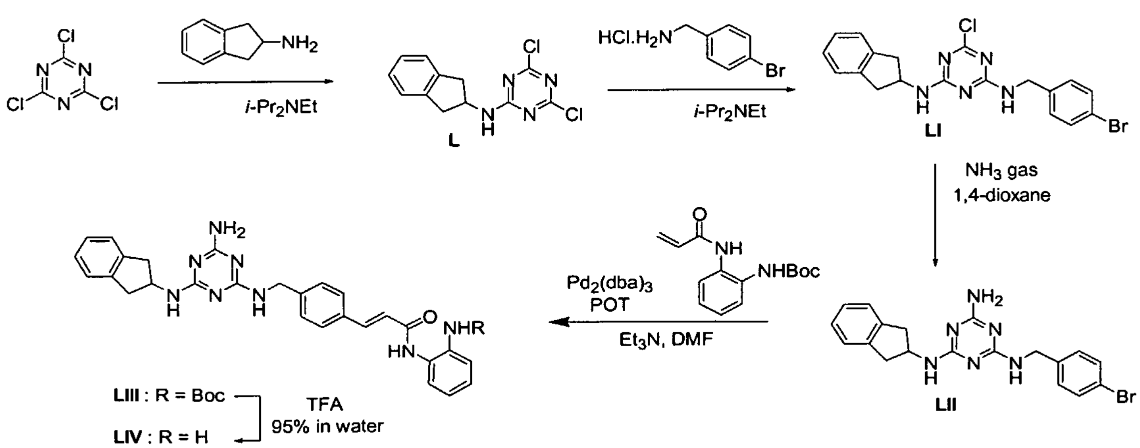
[0198] Compounds such as **XLVII** and **XLIX** preferably may be prepared as outlined in Scheme F. Dibromopyridine is combined with diaminoethane to produce amine **XLIV**. Treatment of amine **XLIV** with isatoic anhydride **LV** in methanol and water, followed by refluxing in formic acid affords compound **XLVI**. Treatment of amine **XLIV** with the reaction products of benzylaminodiacetic acid and acetic anhydride provides compound **XLVIII**. Bromopyridylamines **XLVI** and **XLVIII** are then converted to the corresponding diene anilinylamides **XLVII** and **XLIX**, respectively, by procedures analogous to those set forth in Schemes A-E above.

[0199] Scheme F



[0200] Compounds such as **LIV** preferably may be prepared according to the synthetic route depicted in Scheme G. Trichlorotriazine is treated with aminoindan and diisopropylethylamine to produce dichloroaminotriazine **L**. Treatment with bromobenzylamine and diisopropylethylamine affords diaminochlorotriazine **LI**. Addition of ammonia gas and dioxane provides triaminotriazine **LII**. Treatment with protected acrylanilide, triethylamine, POT, and dibenzylacetone palladium then yields diene anilinylamide **LIII**, which is deprotected with trifluoroacetic acid to provide the final product **LIV**.

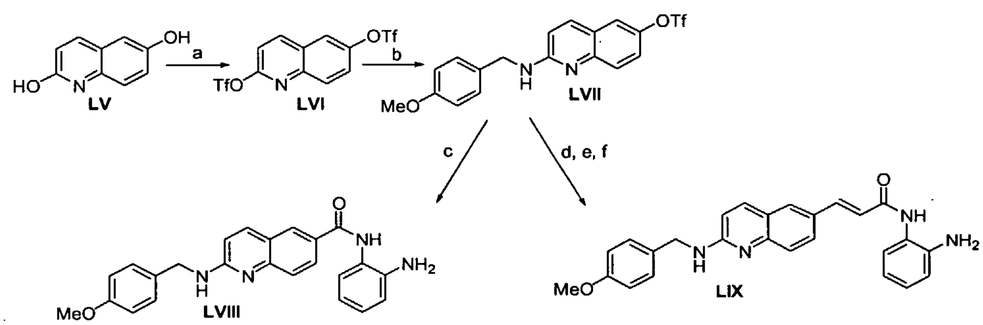
[0201] Scheme G



[0202] Compounds of formula (1), wherein Ar is quinolylene and X comprises -N(R^9)- preferably may be prepared according to the procedures illustrated in Scheme H.

Dihydroxyquinoline LV with dimethylaminopyridine (DMAP) in pyridine is treated with trifluoromethanesulfonic anhydride to provide bis(trifluoromethanesulfonyloxy)-quinoline LVI. Treatment of LVI with p-methoxybenzylamine affords aminoquinoline LVII. Anilinyl amides LVIII and LIX are then prepared using procedures analogous to those described above.

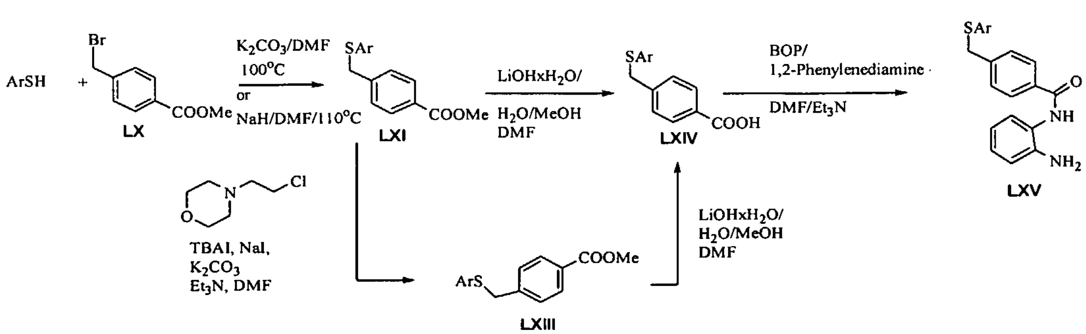
[0203] Scheme H



a. Tf_2O / Py / DMAP / 0 C
b. p-methoxybenzylamine / 120 C
c. 1,2-phenylenediamine / CO (40 psi) / $Pd(OAc)_2$ / dppf / DMF / DIPEA / 70 C
d. t Butylacrylate / $Pd_2(dba)_3$ / POT / DMF / DIPEA / 120 C
e. TFA / DCM / rT
f. 1,2-phenylenediamine / BOP / DMF / TEA / rT

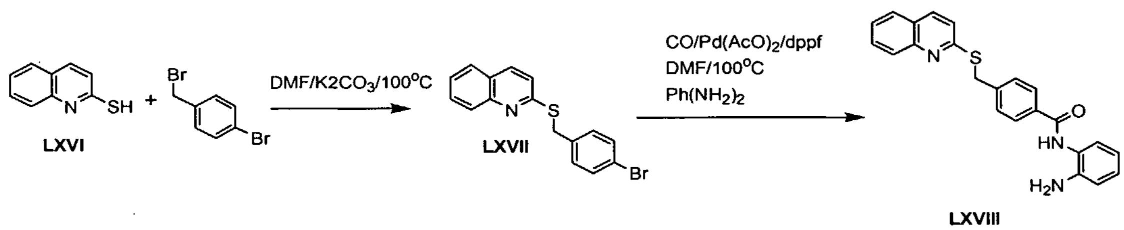
[0204] Compounds wherein X comprises a sulfur atom preferably may be prepared as outlined in Scheme I. Bromide **LX** is converted to diaryl ester **LXI** using procedures analogous to those described for Scheme D above. Ester **LXI** is converted to the corresponding acid **LXIV** by treatment with a hydroxide base, such as lithium hydroxide. Alternatively, ester **LXI** may be treated with chloroethylmorphonline, sodium iodide, potassium carbonate, triethylamine, and tetrabutylammonium iodide (TBAI) in DMF to produce ester **LXIII**, which is then converted to acid **LXIV**. Conversion of the acid **LXIV** to the anilinyl amide **LXV** is effected by treatment of the acid with 1,2-phenylenediamine in the presence of BOP reagent, triethylamine, and dimethylformamide (DMF).

[0205] Scheme I



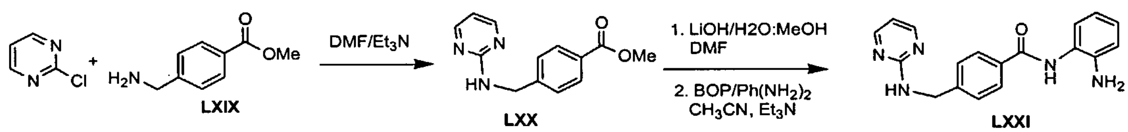
[0206] Alternatively, compounds wherein X comprises a sulfur atom, may be prepared according to the procedures illustrated in Scheme J. Sulfanyl anilinylamide LXVIII is prepared using procedures analogous to those set forth above.

[0207] **Scheme J**



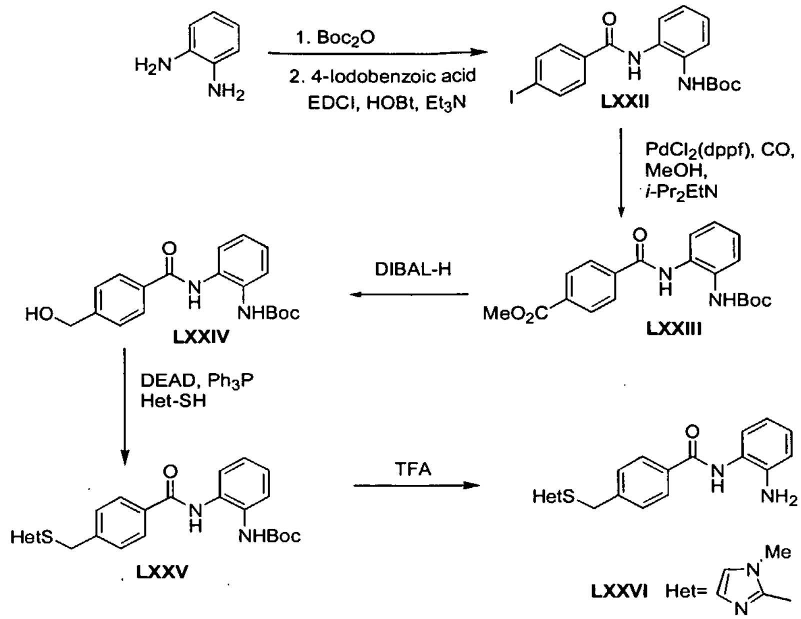
[0208] Compounds wherein X comprises -N(R^9)- preferably may be prepared according to the synthetic route depicted in Scheme K. Amino anilinyl amide **LXXI** is prepared according to synthetic steps similar to those described above.

[0209] **Scheme K**



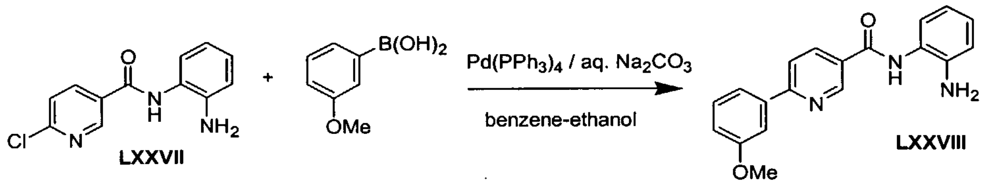
[0210] Compounds wherein X comprises a sulfur atom may be prepared as outlined in Scheme L. Phenylenediamine is reacted with di-tert-butyldicarbonate, followed by iodobenzoic acid, dimethylaminopropylethylcarbodiimide, hydroxybenzotriazole, and triethylamine to provide protected anilinyl amide **LXXII**. The iodide moiety of **LXXII** is converted to the methyl ester moiety of **LXXIII** using procedures analogous to those set forth above. The methyl ester moiety of **LXXIII** is converted to the hydroxyl moiety of **LXXIV** by treatment with a reducing agent such as diisobutylaluminum hydride (DIBAL-H). Addition of the heterocyclylsulfhydryl compound Het-SH with triphenylphosphine and diethylazodicarboxylate converts the hydroxyl moiety of **LXXIV** to the sulfanyl moiety of **LXXV**. **LXXV** is deprotected with trifluoroacetic acid to afford the sulfanyl anilinyl amide **LXXVI**.

[0211] **Scheme L**



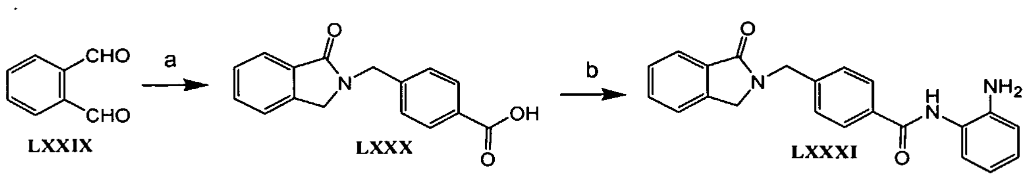
[0212] Compounds wherein X is a chemical bond may be prepared according to the synthetic route depicted in Scheme M. Thus, chloroarylanilinylamide **LXXVII** is treated with aryl boronic acid, benzene, ethanol, aqueous sodium carbonate, and triphenylphosphine palladium to afford the diarylanilinylamide **LXXVIII.**

[0213] Scheme M



[0214] Compounds such as **LXXXI** preferably may be prepared according to the procedues illustrated in Scheme N. Thus, benzene-1,2-carbaldehyde **LXXIX** in acetic acid is treated with p-aminomethylbenzoic acid to produce the benzoic acid **LXXX.** The acid **LXXX** is converted to the corresponding anilinylamide **LXXXI** by treatment with hydroxybenzotriazole, ethylenedichloride, and phenylenediamine.

[0215] Scheme N

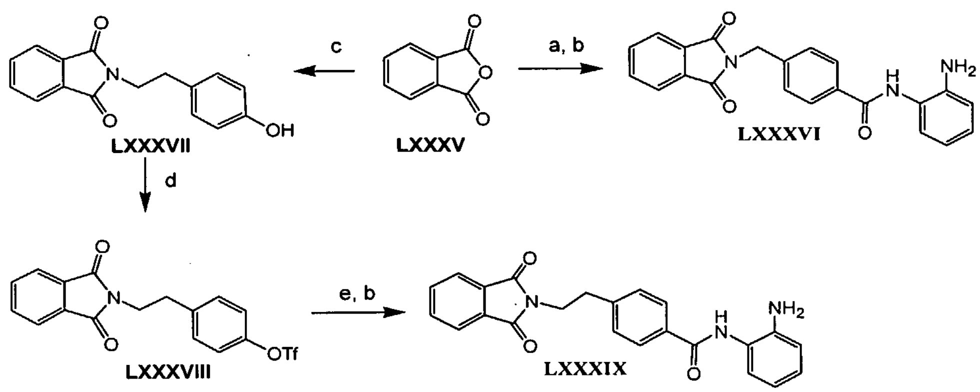


a. p-aminomethylbenzoic acid/AcOH/5 min/reflux
b. HOBT/EDC/1,2-diamino benzene

[0216] Compounds such as **LXXXVI** and **LXXXIX** preferably may be prepared according to the procedures illustrated in Scheme O. Phthalic anhydride **LXXXV** and p-aminomethylbenzoic acid are combined in acetic acid to produce an intermediate carboxylic acid, which is converted to the anilinylamide **LXXXVI** using procedures analogous to those set forth above.

[0217] The addition of 4-(2-aminoethyl)phenol to phthalic anhydride **LXXXV** in acetic acid affords the hydroxyl compound **LXXXVII**. The hydroxyl group of **LXXXVII** is converted to the triflate group of **LXXXVIII** by treatment with sodium hydride, THF, DMF, and phenylaminoditriflate. Treatment of **LXXXVIII** according to procedures analogous to those described for Scheme 3 above affords the anilinylamide **LXXXIX**.

[0218] Scheme O



a. p-aminomethylbenzoic acid/AcOH/reflux/3 hrs
b. HOBT/EDC/1,2-diamino benzene
c. 4-(2-aminoethyl)phenol/AcOH/5 hrs/reflux
d. $PhNTf_2$/NaH/THF-DMF/30 min/0°C
e. 1. CO/$Pd(OAc)_2$/dppf/Et_3N/MeOH-DMF/4 days/75°C
2. AcOH/HCl/3 hrs/reflux

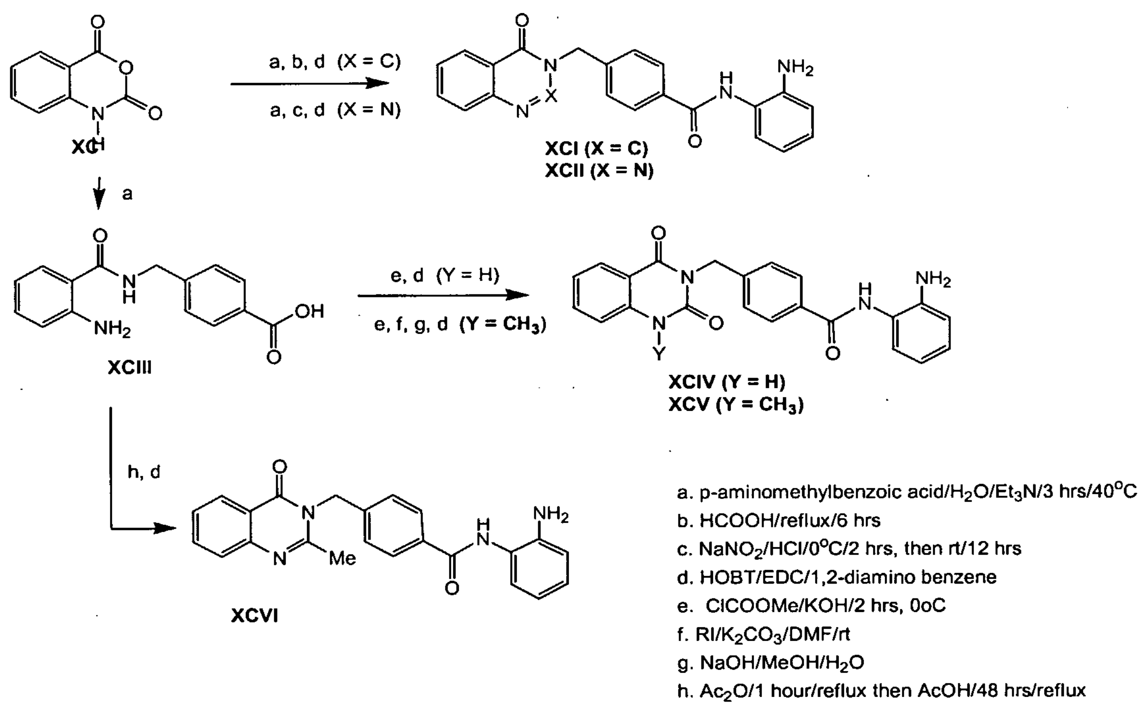
[0219] Compounds such as **XCI-XCVI** preferably may be prepared according to the synthetic route depicted in Scheme P. Treatment of isatoic anhydride **XC** with p-aminomethylbenzoic acid in water and triethylamine, followed by formic acid affords an intermediate carboxylic acid, which is converted to anilinylamide **XCI** using procedures analogous to those described above.

[0220] Alternatively, treatment of isatoic acid **XC** with p-aminomethylbenzoic acid in water and triethylamine, followed by hydrochloric acid and sodium nitrite affords an intermediate carboxylic acid, which is converted to anilinylamide **XCII** using procedures analogous to those described above.

[0221] Alternatively, treatment of isatoic acid **XC** with p-aminomethylbenzoic acid in water and triethylamine affords benzoic acid **XCIII**. Treatment of **XCIII** with sodium hydroxide, dioxane, methylchloroformate, and methanol affords an intermediate quinazolinedione carboxylic acid, the acid moiety of which is then converted to the anilinylamide moiety of **XCIV** using procedures analogous to those described above. Alternatively, the intermediate quanzolinedione carboxylic acid in DMF is treated with potassium carbonate and methyl iodide to produce an intermediate benzoic acid methyl ester, which is converted to an intermediate benzoic acid by treatment with sodium hydroxide, methanol, and water. The benzoic acid is then converted to the corresponding anilinylamide **XCV** using procedures analogous to those described above.

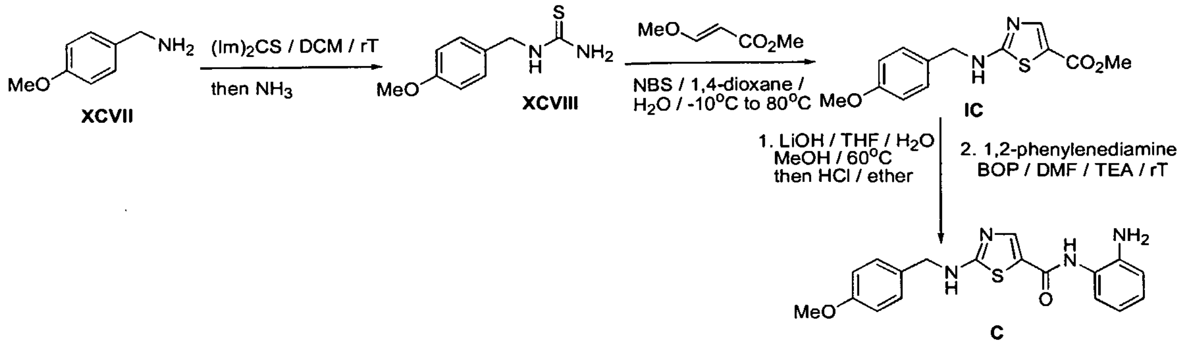
[0222] Alternatively, treatment of **XCIII** with acetic anhydride followed by acetic acid produces an intermediate carboxylic acid, which is converted to anilinylamide **XCVI** using procedures analogous to those described above.

[0223] **Scheme P**



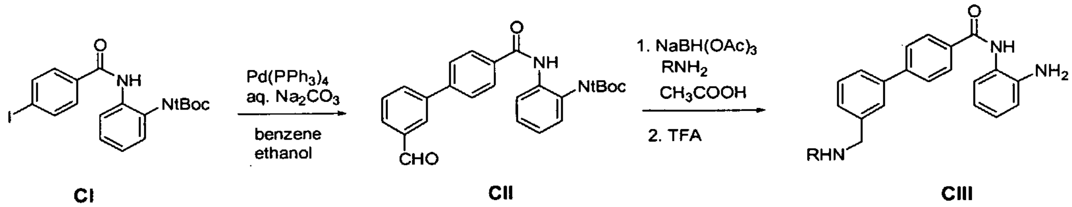
[0224] Compounds such as **C** preferably may be prepared as outlined in Scheme Q. Alkylamine **XCVII** is treated with thiocarbonyl diimidazole in dichloromethane, followed by ammonium hydroxide to afford thiourea **XCVIII**. Treatment of thiourea **XCVIII** with methylmethoxyacrylate in dioxane and N-bromosuccinimide produces thiazole ester **IC**. The ester **IC** is converted to the corresponding anilinylamine **C** using procedures analogous to those set forth above.

[0225] Scheme Q



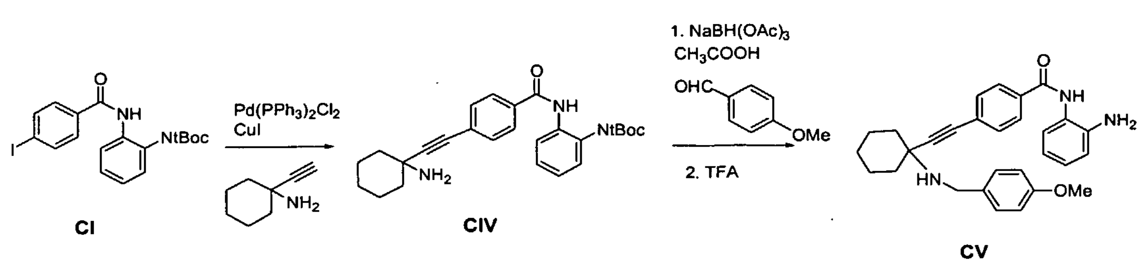
[0226] Compounds wherein X is a chemical bond and Cy has an amino substituent may be prepared according to the synthetic route depicted in R. Thus, protected iodoarylanilinylamide CI is treated according to procedures analogous to those described above to afford the diarylanilinylamide CII. The aldehyde moiety in CII is converted to the corresponding secondary amine moiety by treatment with the primary amine and sodium triacetoxyborohydride followed by glacial acetic acid. The resultant compound is deprotected to yield CIII using procedures analogous to those set forth in above.

[0227] Scheme R

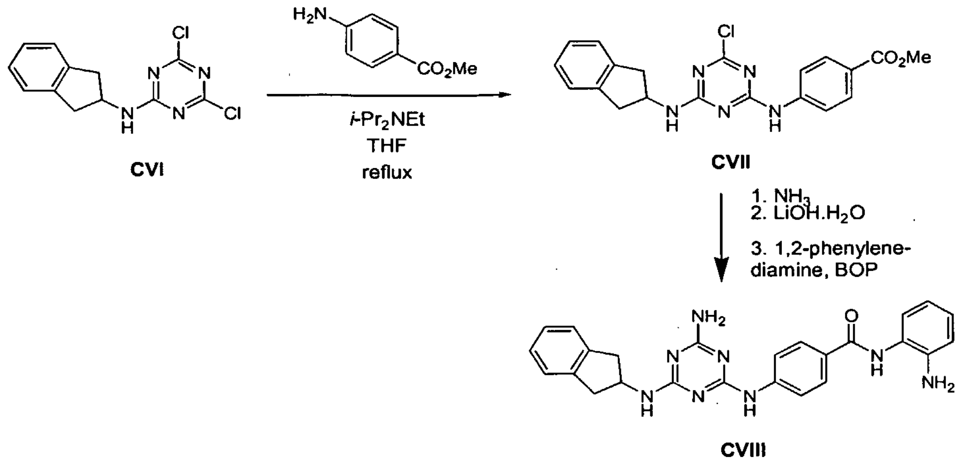


[0228] Compounds wherein X comprises an alkynylene moiety may be prepared as outlined in Scheme S. Treatment of protected iodoarylanilinylamide CI with triphenylphosphine palladium chloride, cuprous iodide, and 1-ethynylcyclohexylamine affords the alkynylarylanilinylamide CIV. The primary amine moiety in CIV is converted to the corresponding secondary amine and the aniline moiety is deprotected to afford CV using procedures analogous to those described above.

[0229] Scheme S

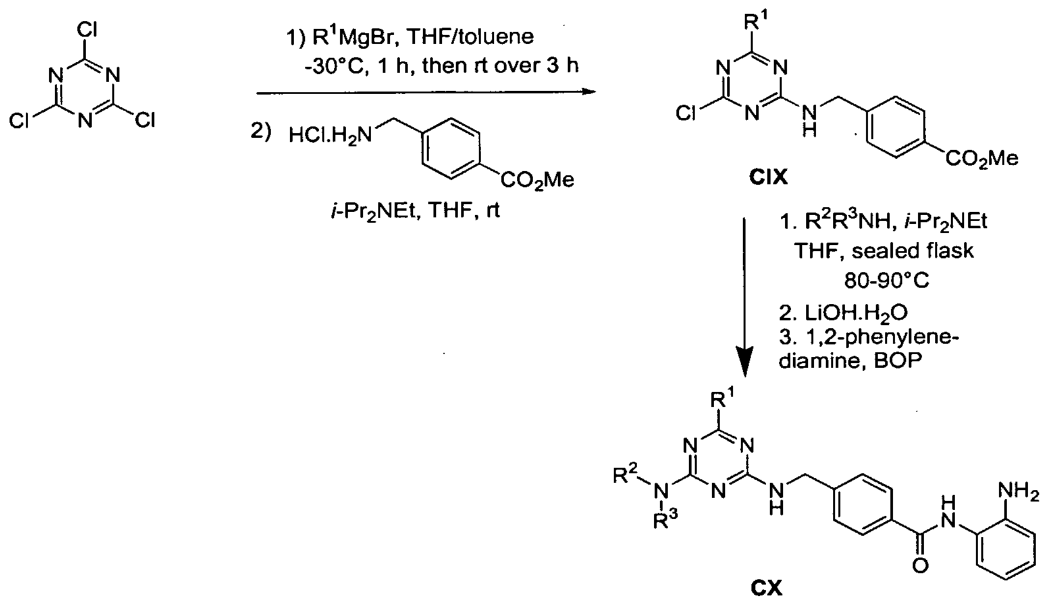


[0230] Scheme T



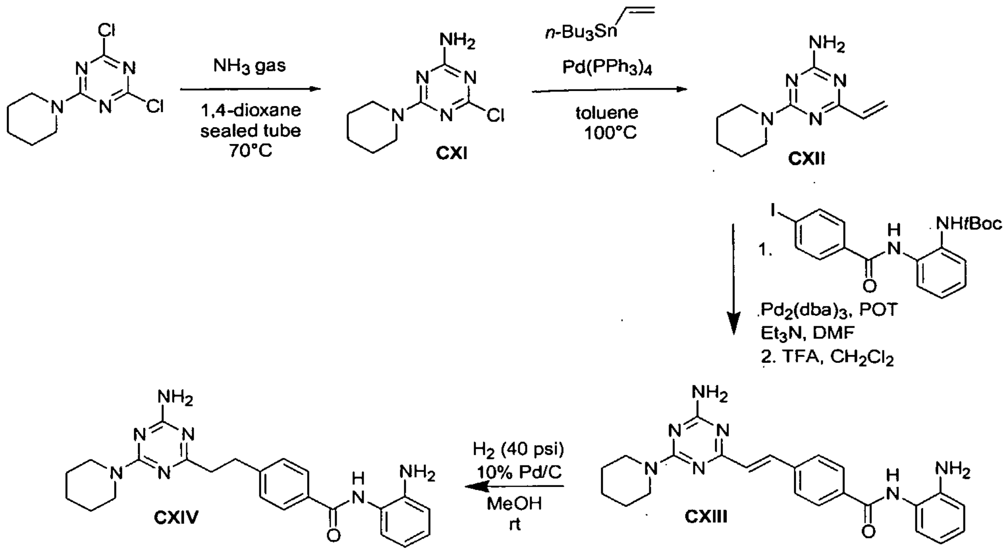
[0231] Compounds such as **CVIII** preferably may be prepared according to the synthetic route depicted in Scheme T. Dichloroaminotriazine **CVI** is treated with methyl-4-aminobenzoate in the presence of diisopropylethylamine to produce diaminotriazine **CVII**. Addition of ammonia gas and dioxane, followed by a saponification and a peptide coupling to yield **CVIII**.

[0232] Scheme U



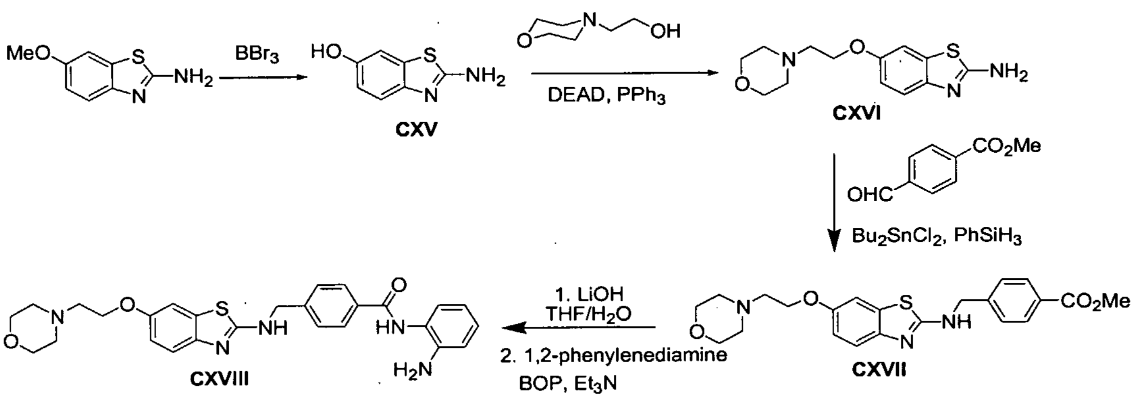
[0233] Compounds such as **CX** preferably may be prepared according to the synthetic route depicted in Scheme U. The Grignard reaction of trichloroaminotriazine with various alkyl magnesium bromide, followed by a treatment with methyl-4-aminobenzoate in the presence of diisopropylethylamine yields alkylaminotriazine **CIX**. Synthetic methods similar to those set forth above are then used to convert ester **CIX** to the corresponding anilinyl amide **CX**.

[0234] Scheme V



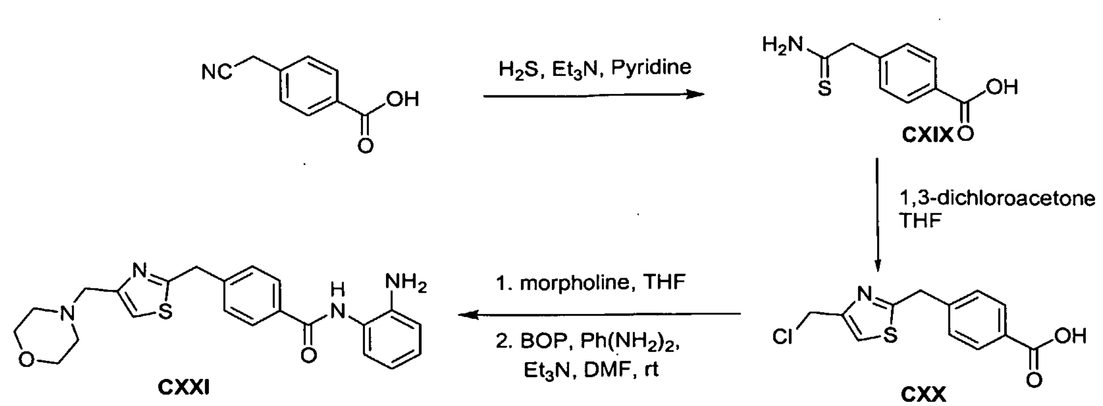
[0235] As shown in Scheme V, amination of dichlorotriazine affords **CXI**. Stille coupling using vinyl stannane provides **CXII**. Treatment with protected iodoanilide, triethylamine, POT and dibenzylacetone palladium then yields anilinylamide, which is deprotected with trifluoroacetic acid to provide the alkene **CXIII**. Hydrogenation of the alkene affords the final compound **CXIV**.

[0236] Scheme W



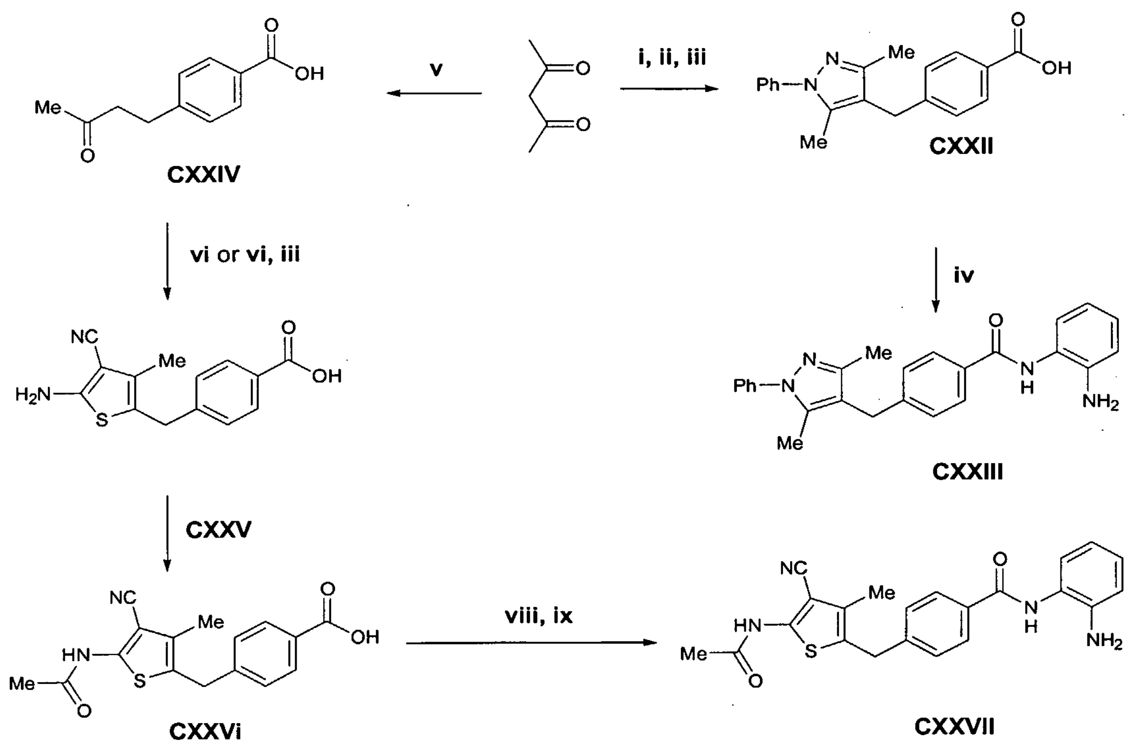
[0237] Compounds such as **CXVIII** preferably may be prepared according to the synthetic route depicted in Scheme W. Treatment of methoxyaminobenzothiazole with tribromide boron affords the corresponding acid **CXV**. Mitsunobu reaction using hydroxyethyl morpholine in the presence of diethylazodicarboxylate and triphenylphosphine yields the amine **CXVI**. Reductive amination with methyl-4-formylbenzoate using phenylsilane and tin catalyst yields to the ester **CXVII**. Saponification followed by the usual peptide coupling analogous to those described above provides the desired anilide **CXVIII**.

[0238] Scheme X



[0239] Treatment 4-methylcyanobenzoic acid with hydrogen sulfide affords **CXIX**, which is subjected to cyclization in the presence of 1,3-dichloroacetone to yield **CXX**. Treatment with morpholine followed by a peptide coupling using the standard condition produces **CXXI**.

[0240] **Scheme Y**

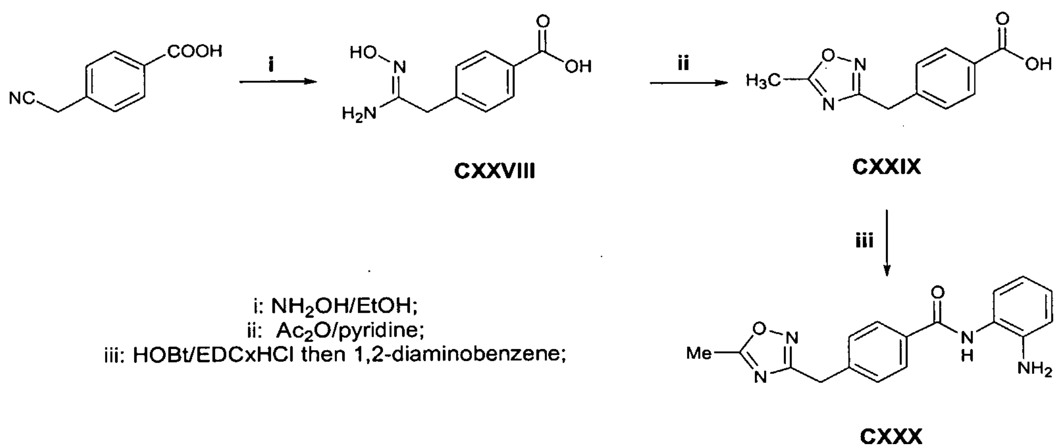


i: $BrCH_2C_6H_4COOMe/MeONa/THF$;
ii: $PhNHNH_2$;
iii: NaOH, then HCl
iv: HOBt/EDCxHCl then 1,2-diaminobenzene;
v: $BrCH_2C_6H_4COOMe/MeONa/MeOH$, then HCl/AcOH;
vi: $CH_2(CN)_2/S_8/Et_2NH$;
vii: AcCl;
viii: 2-N-Bocamino aniline;
ix: TFA;

[0241] Compounds such as **CXXIII** and **CXXVII** preferably may be prepared according to the synthetic scheme Y. Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and phenyl hydrazine followed by saponification, afforded the intermediate acid **CXXII**. This material was coupled with 1,2-diaminobenzene in a standard fashion to afford **CXXIII**.

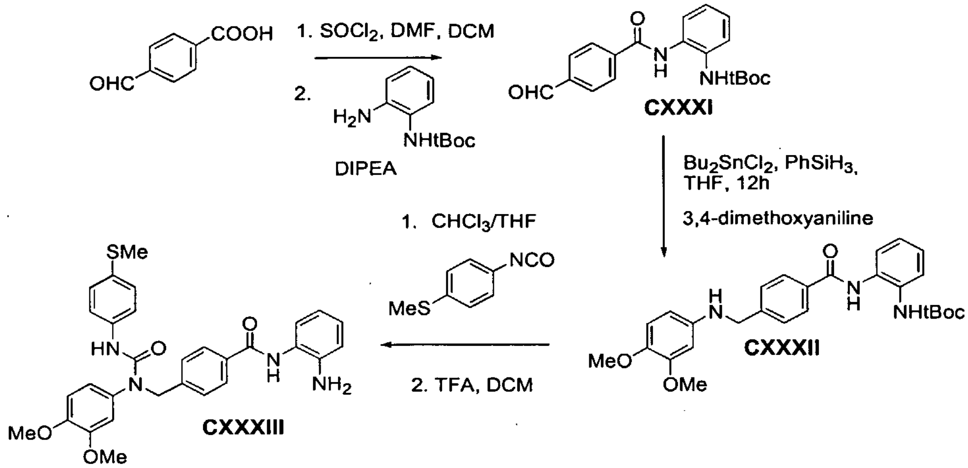
[0242] Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and a 1:1 mixture AcOH-HCl (conc.) afforded the intermediate acid **CXXIV**. This keto-acid reacting with sulfur and malonodinitrile in the presence of a base, produced the thiophene **CXXV**, which was converted into the desired **CXXVII** using standard procedures.

[0243] Scheme Z



[0244] Compounds such as CXXX preferably may be prepared according to the synthetic scheme Z. Treatment of 4-cyanomethylbenzoic acid with hydroxylamine produced the amidoxime CXXVIII, which upon treatment with acetic anhydride was converted into the oxadiazole CXXIX. The latter was coupled with 1,2-diaminobenzene in a standard fashion to afford CXXX.

[0245] Scheme AA



[0246] Compounds such as CXXXIII preferably may be prepared according to the synthetic route depicted in Scheme AA. Treatment of 4-formylbenzoic acid with thionyl chloride afford the acyl chloride which is coupled with protected anilide to produce CXXXI. Reductive amination with dimethoxyaniline using phenylsilane and tin catalyst yields to the protected anilide CXXXII. Treatment with isocyanate followed by deprotection with trifluoroacetic acid provides the ureidoanilide CXXXIII.

Pharmaceutical Compositions

[0247] In a second aspect, the invention provides pharmaceutical compositions comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0248] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of

pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

[0249] As used herein, the term pharmaceutically acceptable salts refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula -NR + Z-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

[0250] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

Inhibition of Histone Deacetylase

[0251] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase according to the invention. Because compounds of the invention inhibit histone deacetylase, they are useful research tools for *in vitro* study of the role of histone deacetylase in biological processes. In addition, the compounds of the invention selectively inhibit certain isoforms of HDAC.

[0252] Measurement of the enzymatic activity of a histone deacetylase can be achieved using known methodologies. For example, Yoshida et al., J. Biol. Chem., **265**: 17174-17179 (1990), describes the assessment of histone deacetylase enzymatic activity by the detection of acetylated histones in trichostatin A treated cells. Taunton et al., Science, **272**: 408-411 (1996), similarly describes methods to measure histone deacetylase enzymatic activity using endogenous and recombinant HDAC-1.

[0253] In some preferred embodiments, the histone deacetylase inhibitor interacts with and reduces the activity of all histone deacetylases in the cell. In some other preferred embodiments according to this aspect of the invention, the histone deacetylase inhibitor interacts with and reduces the activity of fewer than all histone deacetylases in the cell. In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1) or a sub-group of histone deacetylases (e.g., HDAC-1, HDAC-2, and HDAC-3) to a greater extent than other histone deacetylases. Where the inhibitor preferentially reduces the activity of a sub-group of histone deacetylases, the reduction in activity of each member of the sub-group may be the same or different. As discussed below, certain particularly preferred histone deacetylase inhibitors are those that interact with, and reduce the enzymatic activity of, histone deacetylases that are involved in tumorigenesis. Certain other preferred histone deacetylase inhibitors interact with and reduce the enzymatic activity of fungal histone deacetylases.

[0254] Preferably, the method according to the third aspect of the invention causes an inhibition of cell proliferation of the contacted cells. The phrase "inhibiting cell proliferation" is used to denote an ability of an inhibitor of histone deacetylase to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter, Miami, FL) or a hemacytometer. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells.

[0255] Preferably, growth of cells contacted with the inhibitor is retarded by at least 50% as compared to growth of non-contacted cells. More preferably, cell proliferation is inhibited by 100% (i.e., the contacted cells do not increase in number). Most preferably, the phrase "inhibiting cell proliferation" includes a reduction in the number or size of contacted cells, as compared to non-contacted cells. Thus, an inhibitor of histone deacetylase according to the invention that

inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., to apoptose), or to undergo necrotic cell death.

[0256] The cell proliferation inhibiting ability of the histone deacetylase inhibitors according to the invention allows the synchronization of a population of asynchronously growing cells. For example, the histone deacetylase inhibitors of the invention may be used to arrest a population of non-neoplastic cells grown in vitro in the G1 or G2 phase of the cell cycle. Such synchronization allows, for example, the identification of gene and/or gene products expressed during the G1 or G2 phase of the cell cycle. Such synchronization of cultured cells may also be useful for testing the efficacy of a new transfection protocol, where transfection efficiency varies and is dependent upon the particular cell cycle phase of the cell to be transfected. Use of the histone deacetylase inhibitors of the invention allows the synchronization of a population of cells, thereby aiding detection of enhanced transfection efficiency.

[0257] In some preferred embodiments, the contacted cell is a neoplastic cell. The term "neoplastic cell" is used to denote a cell that shows aberrant cell growth. Preferably, the aberrant cell growth of a neoplastic cell is increased cell growth. A neoplastic cell may be a hyperplastic cell, a cell that shows a lack of contact inhibition of growth in vitro, a benign tumor cell that is incapable of metastasis in vivo, or a cancer cell that is capable of metastasis in vivo and that may recur after attempted removal. The term "tumorigenesis" is used to denote the induction of cell proliferation that leads to the development of a neoplastic growth. In some embodiments, the histone deacetylase inhibitor induces cell differentiation in the contacted cell. Thus, a neoplastic cell, when contacted with an inhibitor of histone deacetylase may be induced to differentiate, resulting in the production of a non-neoplastic daughter cell that is phylogenetically more advanced than the contacted cell.

[0258] In some preferred embodiments, the contacted cell is in an animal. Thus, the invention provides a method for treating a cell proliferative disease or condition in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably, the animal is a mammal, more preferably a domesticated mammal. Most preferably, the animal is a human.

[0259] The term "cell proliferative disease or condition" is meant to refer to any condition characterized by aberrant cell growth, preferably abnormally increased cellular proliferation. Examples of such cell proliferative diseases or conditions include, but are not limited to, cancer, restenosis, and psoriasis. In particularly preferred embodiments, the invention provides a

method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a histone deacetylase inhibitor of the invention.

[0260] It is contemplated that some compounds of the invention have inhibitory activity against a histone deacetylase from a protozoal source. Thus, the invention also provides a method for treating or preventing a protozoal disease or infection, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a protozoal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0261] The present invention further provides a method for treating a fungal disease or infection comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a fungal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0262] The term "therapeutically effective amount" is meant to denote a dosage sufficient to cause inhibition of histone deacetylase activity in the cells of the subject, or a dosage sufficient to inhibit cell proliferation or to induce cell differentiation in the subject. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0263] When administered systemically, the histone deacetylase inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about 0.01 μM to about 100 μM, more preferably from about 0.05 μM to about 50 μM, still more preferably from about 0.1 μM to about 25 μM, and still yet more preferably from about 0.5 μM to about 25 μM. For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of histone deacetylase inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

[0264] In certain preferred embodiments of the third aspect of the invention, the method further comprises contacting the cell with an antisense oligonucleotide that inhibits the expression of a histone deacetylase. The combined use of a nucleic acid level inhibitor (e.g., antisense oligonucleotide) and a protein level inhibitor (i.e., inhibitor of histone deacetylase enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonucleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC7, and/or HDAC-8 (see e.g., GenBank Accession Number U50079 for HDAC-1, GenBank Accession Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

[0265] For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 6 to about 100 nucleoside residues, more preferably from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleoside linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/ or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane.

[0266] For purposes of the invention the term "2'-substituted ribonucleoside" includes ribonucleosides in which the hydroxyl group at the 2' position of the pentose moiety is substituted to produce a 2'-O-substituted ribonucleoside. Preferably, such substitution is with a lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be unsubstituted or may be substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl, or amino groups. The term "2'-substituted ribonucleoside" also includes

ribonucleosides in which the 2'-hydroxyl group is replaced with an amino group or with a halo group, preferably fluoro.

[0267] Particularly preferred antisense oligonucleotides utilized in this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

[0268] For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see e.g., Pederson et al. U.S. Patent Nos. 5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

[0269] For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide contains at least three consecutive deoxyribonucleosides and also contains ribonucleosides, 2'-substituted ribonucleosides, preferably 2'-O-substituted ribonucleosides, or combinations thereof (see e.g., Metelev and Agrawal, U.S. Patent No. 5,652,355).

[0270] The exact nucleotide sequence and chemical structure of an antisense oligonucleotide utilized in the invention can be varied, so long as the oligonucleotide retains its ability to inhibit expression of the gene of interest. This is readily determined by testing whether the particular antisense oligonucleotide is active. Useful assays for this purpose include quantitating the mRNA encoding a product of the gene, a Western blotting analysis assay for the product of the gene, an activity assay for an enzymatically active gene product, or a soft agar growth assay, or a reporter gene construct assay, or an in vivo tumor growth assay, all of which are described in detail in this specification or in Ramchandani et al. (1997) Proc. Natl. Acad. Sci. USA 94: 684-689.

[0271] Antisense oligonucleotides utilized in the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (i.e., H-phosphonate chemistry for some cycles and phosphoramidite

chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG) (see, e.g., Pon, R.T. (1993) Methods in Molec. Biol. 20: 465-496).

[0272] Particularly preferred oligonucleotides have nucleotide sequences of from about 13 to about 35 nucleotides which include the nucleotide sequences shown in Table A. Yet additional particularly preferred oligonucleotides have nucleotide sequences of from about 15 to about 26 nucleotides of the nucleotide sequences shown in Table A.

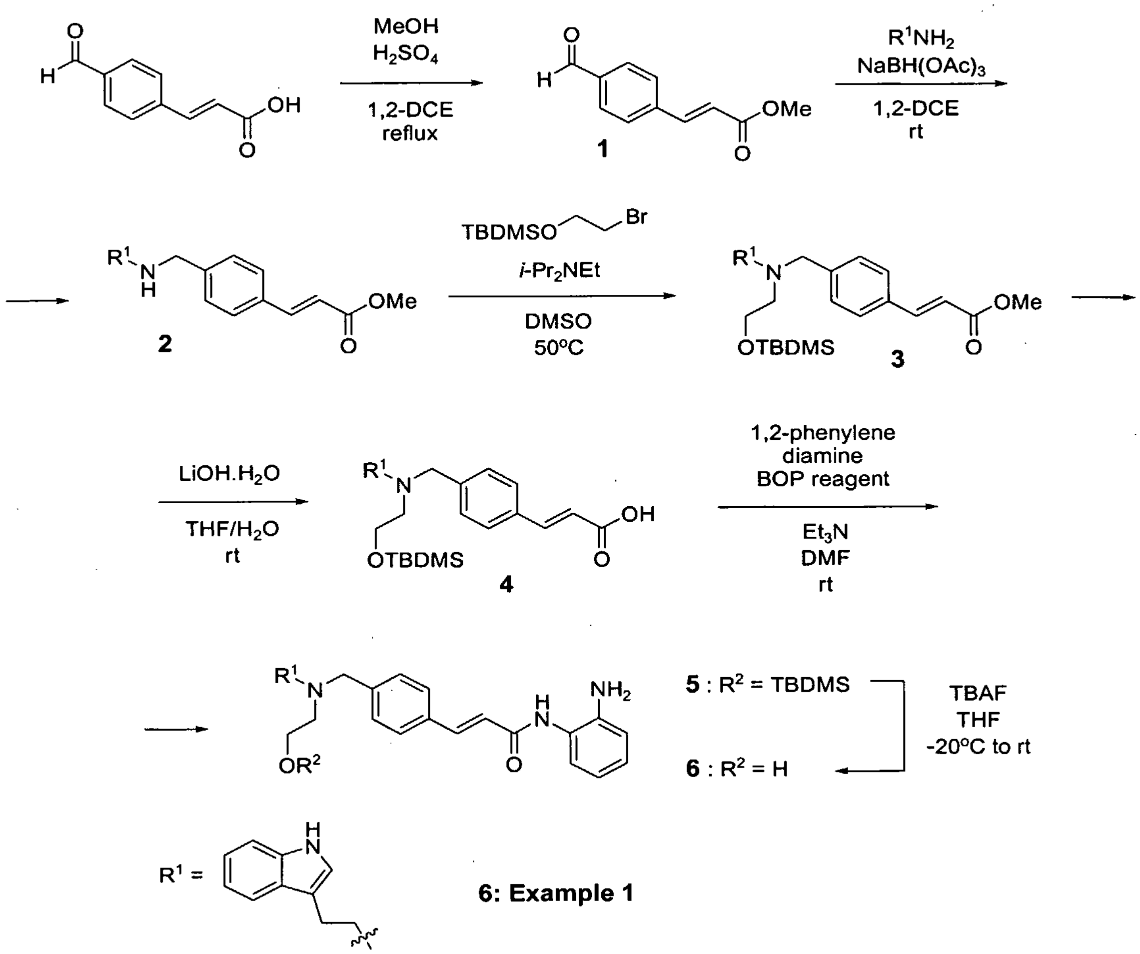
Table A

Oligo	Target	Accession Number	Nucleotide Position	Sequence	position within Gene
HDAC1 AS1	Human HDAC1	U50079	1585-1604	5'-GAAACGTGAGGGACTCAGCA-3'	3'-UTR
HDAC1 AS2	Human HDAC1	U50079	1565-1584	5'-GGAAGCCAGAGCTGGAGAGG-3'	3'-UTR
HDAC1 MM	Human HDAC1	U50079	1585-1604	5'-GTTAGGTGAGGCACTGAGGA-3'	3'-UTR
HDAC2 AS	Human HDAC2	U31814	1643-1622	5'-GCTGAGCTGTTCTGATTTGG-3'	3'-UTR
HDAC2 MM	Human HDAC2	U31814	1643-1622	5'-CGTGAGCACTTCTCATTTCC-3'	3'-UTR
HDAC3 AS	Human HDAC3	AF039703	1276-1295	5'-CGCTTTCCTTGTCATTGACA-3'	3'-UTR
HDAC3 MM	Human HDAC3	AF039703	1276-1295	5'-GCCTTTCCTACTCATTGTGT-3'	3'-UTR
HDAC4 AS1	Human HDAC4	AB006626	514-33	5-GCTGCCTGCCGTGCCCACCC-3'	5'-UTR
HDAC4 MM1	Human HDAC4	AB006626	514-33	5'-CGTGCCTGCGCTGCCCACGG-3'	5'-UTR
HDAC4 AS2	Human HDAC4	AB006626	7710-29	5'-TACAGTCCATGCAACCTCCA-3'	3'-UTR
HDAC4 MM4	Human HDAC4	AB006626	7710-29	5'-ATCAGTCCAACCAACCTCGT-3'	3'-UTR
HDAC5 AS	Human HDAC5	AF039691	2663-2682	5'-CTTCGGTCTCACCTGCTTGG-3'	3'-UTR
HDAC6 AS	Human HDAC6	AJ011972	3791-3810	5'-CAGGCTGGAATGAGCTACAG-3'	3'-UTR
HDAC6 MM	Human HDAC6	AJ011972	3791-3810	5'-GACGCTGCAATCAGGTAGAC-3'	3'-UTR
HDAC7 AS	Human HDAC7	AF239243	2896-2915	5'-CTTCAGCCAGGATGCCCACA-3'	3'-UTR
HDAC8 AS1	Human HDAC8	AF230097	51-70	5'-CTCCGGCTCCTCCATCTTCC-3'	5'-UTR
HDAC8 AS2	Human HDAC8	AF230097	1328-1347	5'-AGCCAGCTGCCACTTGATGC-3'	3'-UTR

[0273] The following examples are intended to further illustrate certain preferred embodiments of the invention, and are not intended to limit the scope of the invention.

EXAMPLES

Scheme 1



6: Example 1

Example 1:

N-(2-Amino-phenyl)-3-[4-({(2-hydroxy-ethyl)-[2-(1*H*-indol-3-yl)-ethyl]-amino}-methyl)-phenyl]-acrylamide (6)

[0274] Step 1: Methyl 3-(4-formyl-phenyl)-acrylate (1)

[0275] To a stirred suspension at room temperature of 4-formylcinnamic acid (15.39 g, 87.36 mmol) in 1,2-dichloroethane (100 mL) was added concentrated sulfuric acid (8 mL) and anhydrous MeOH (15 mL), respectively. The reaction mixture was refluxed for 18 h, cooled to the room temperature and concentrated. The residue was diluted with AcOEt and washed with H_2O, saturated aqueous $NaHCO_3$, H_2O and brine, dried over $MgSO_4$, filtered, and concentrated again. The crude product was purified by flash chromatography on silica gel (eluent AcOEt/hexane:

20/80→30/70) to afford the title compound **2** (9.75 g, 51.26 mmol, 59% yield) as a pale yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 10.04 (s, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.80-7.60 (m, 3H), 6.56 (d, J = 15.8 Hz, 1H), 3.84 (s, 3H).

[0276] Step 2: Methyl 3-(4-{[2-(1H-indol-3-yl)-ethylamino]-methyl}-phenyl)-acrylate (2)

[0277] To a stirred solution of **1** (3.00 g, 15.77 mmol) and tryptamine (2.78 g, 17.35 mmol) in anhydrous 1,2-dichloroethane (200 mL) under nitrogen was added $NaBH(OAc)_3$ (3.87 g, 17.35 mmol) at room temperature. The reaction mixture was stirred at room temperature for 39 hours, poured into 10% solution of K_2CO_3 and extracted with CH_2Cl_2. The organic layer was concentrated to form a residue which was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$, 10/90) and co-precipitated in a mixture of AcOEt/hexane to afford the title compound **2** (4.39 g, 13.13 mmol, 83% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 10.78 (s, 1H), 7.70-7.62 (m, 3H), 7.49 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.33 (dt, J = 8.0, 0.9 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 7.06 (ddd, J = 7.0, 7.0, 1.2 Hz, 1H), 6.96 (ddd, J = 6.9, 6.9, 1.1 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 3.79 (s, 2H), 3.75 (s, 3H), 2.91-2.78 (m, 4H), 2.18 (bs,1H).

[0278] Step 3: Methyl 3-[4-({[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amino}-methyl)-phenyl]-acrylate (3)

[0279] To a stirred solution of **2** (2.82 g, 8.44 mmol) and diisopropylethylamine (2.21 mL, 12.66 mmol) in anhydrous DMSO (22 mL) at room temperature under nitrogen was added (2-bromo-ethoxy)-*tert*-butyl-dimethylsilane (2.17 mL, 10.12 mmol). The reaction mixture was heated at 50-55□C for 24 h, poured into water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel ($AcOEt/CH_2Cl_2$, 15/85, plus a few drops of NH_4OH) to afford the title compound **3** (4.06 g, 8.24 mmol, 97% yield) as a dark orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.95 (bs, 1H), 7.70 (d, J = 15.8 Hz, 1H), 7.58-7.30 (m, 6H), 7.18 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.00 (bs, 1H), 6.43 (d, J = 16.2 Hz, 1H), 3.88-3.68 (m, 7H), 3.04-2.66 (m, 6H), 0.88 (bs,9H), 0.04 (bs, 6H).

[0280] Step 4: 3-[4-({[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amino}-methyl)-phenyl]-acrylic acid (4)

[0281] To a stirred solution of compound **3** (3.18 g, 6.45 mmol) in THF (40 mL) was added a solution of $LiOH.H_2O$ (677 mg, 16.14 mmol) in water (20 mL) at room temperature. After 24 h the reaction mixture was concentrated, diluted with water and acidified with 1N HCl until a pH 5-6. A precipitate was formed which was separated by filtration, rinsed with water and dried to afford

the title compound **4** (2.43 g, 5.08 mmol, 79% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 12.34 (bs, 1H), 10.75 (s, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.44-7.35 (m, 3H), 7.32 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 2.3 Hz, 1H), 7.05 (td, J = 7.5, 1.0 Hz, 1H), 6.92 (td, J = 7.4, 0.9 Hz, 1H), 6.51 (d, J = 15.8 Hz, 1H), 3.79 (s, 2H), 3.69 (t, J = 6.4 Hz, 2H), 2.93-2.74 (m, 4H), 2.69 (t, J = 6.2 Hz, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

[0282] Step 5: N-(2-Amino-phenyl)-3-[4-({[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-[2-(1H-indol-3-yl)-ethyl]-amino}-methyl)-phenyl]-acrylamide (5)

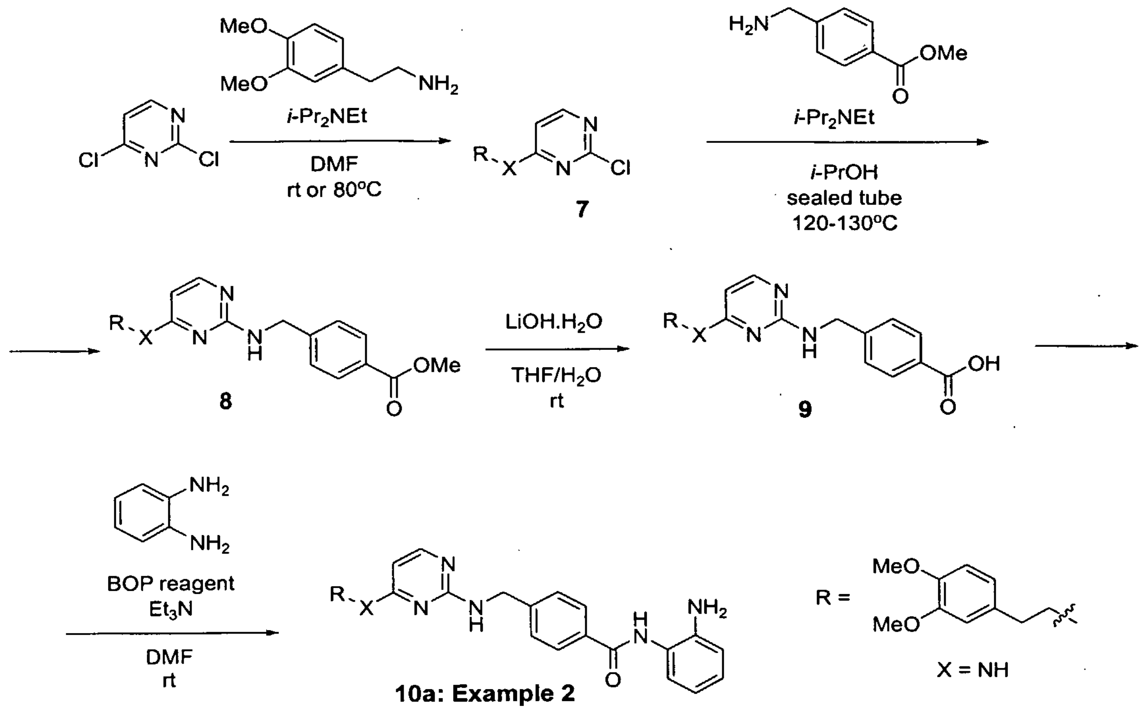
[0283] To a stirred solution of **4** (1.30 g, 2.72 mmol) in anhydrous DMF (20 mL) at room temperature under nitrogen were added Et_3N (330 µl, 3.26 mmol) and BOP reagent (1.32 g, 2.99 mmol), respectively. After 30 min, a solution of 1,2-phenylenediamine (352 mg, 3.26 mmol), Et_3N (1.14 mL, 8.15 mmol) in anhydrous DMF (3 mL) was added dropwise. After 3 h the reaction mixture was poured into saturated aqueous solution of NH_4Cl, and extracted with AcOEt. The extract was washed with saturated NH_4Cl, water and brine, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography on silica gel (MeOH/CH_2Cl_2, 5/95 plus several drops of NH_4OH), to afford the title compound **5** (1.49 g, 2.62 mmol, 96% yield) as a yellow sticky foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ(ppm) : 10.78 (s, 1H), 9.40 (s, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 15.8 Hz, 1H), 7.45 (d, J = 7.9 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.14 (s, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.05-6.85 (m, 3H), 6.79 (d, J = 7.9 Hz, 1H), 6.62 (t, J = 7.5 Hz, 1H), 4.98 (bs, 2H), 3.80 (s, 2H), 3.71 (t, J = 6.2 Hz, 2H), 2.95-2.75 (m, 4H), 2.71 (t, J = 6.2 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

[0284] Step 6: N-(2-Amino-phenyl)-3-[4-({(2-hydroxy-ethyl)-[2-(1H-indol-3-yl)-ethyl]-amino}-methyl)-phenyl]-acrylamide (6)

[0285] To a stirred solution at –20□C of **5** (1.49 g, 2.62 mmol) in anhydrous THF (30 mL) under nitrogen was slowly added a solution of TBAF (2.88 mL, 2.88 mmol, 1.0M in THF). The reaction mixture was allowed to warm-up to the room temperature over 1 h and was stirred for additional 22 hours. MeOH was added and the reaction mixture was concentrated, diluted with AcOEt, and successively washed with saturated aqueous solution of $NaHCO_3$, H_2O, a saturated aqueous solution of NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (MeOH/CH_2Cl_2, 5/95→10/90 plus several drops of NH_4OH) and triturated with a mixture of AcOEt/CH_2Cl_2/hexane to afford the title compound **6** (956 mg, 2.10 mmol, 80% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.76 (s, 1H), 9.39 (s, 1H), AB system (δ_A = 7.58, δ_B = 7.44, J_{AB} = 8.0 Hz, 4H), 7.56 (d, J = 15.7 Hz, 1H), 7.42-7.34 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 7.05

(td, J = 7.2, 1.2 Hz, 1H), 6.98-6.90 (m, 2H), 6.90 (d, J = 15.8 Hz, 1H), 6.77 (dd, J = 8.0,1.4 Hz, 1H), 6.60 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 4.98 (bs, 2H), 4.43 (t, J = 5.4 Hz, 1H), 3.78 (s, 2H), 3.56 (td, J = 6.3, 5.6 Hz, 2H), 2.94-2.84 (m, 2H), 2.82-2.74 (m, 2H), 2.68 (t, J = 6.5 Hz, 2H).

Scheme 2



Example 2:

N-(2-Amino-phenyl)-4-({4-[2-(3,4-dimethoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-methyl)-benzamide (10a)

[0286] Step 1: (2-Chloro-pyrimidin-4-yl)-[2-(3,4-dimethoxy-phenyl)-ethyl]-amine (7)

[0287] To a stirred solution of 2,4-dichloropyrimidine (500 mg, 3.36 mmol) in anhydrous DMF (10 mL) at room temperature under nitrogen were slowly added i-Pr_2NEt (1.06 mL, 6.10 mmol) and 3,4-dimethoxyphenethylamine (531 µl, 3.05 mmol), respectively. After 24 h the reaction mixture was diluted with AcOEt and successively washed with saturated aqueous solution of NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 2/98→5/95) to afford the title compound **7a** (744 mg, 2.53 mmol, 83% yield) as pale yellow oil.

[0288] Step 2: Methyl 4-({4-[2-(3,4-dimethoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-methyl)-benzoate (8)

[0289] In a sealed flask, a mixture of **7** (744 mg, 2.53 mmol), methyl 4-(aminomethyl)benzoate (628 mg, 3.80 mmol) and i-Pr_2NEt (882 µl, 5.07 mmol) in isopropanol (50

mL) was heated to 120-125□C for 7 days (during this period of time an excess of methyl 4-(aminomethyl)benzoate was added to the reaction mixture). The reaction mixture was allowed to cool to the room temperature, concentrated and purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$, 5/95→10/90 plus several drops of NH_4OH) to afford the title compound **8** (671 mg, 1.59 mmol, 63% yield) as an orange sticky solid.

[0290] Step 3: 4-({4-[2-(3,4-Dimethoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-methyl)-benzoic acid (9)

[0291] To a stirred solution of compound **8** (670 mg, 1.59 mmol) in THF (15 mL) at room temperature was added a solution of $LiOH.H_2O$ (166 mg, 3.97 mmol) in water (5 mL). After 24 h, the reaction mixture was concentrated, diluted with water and acidified with 2N HCl (pH at 5-6). A precipitate formed, which was separated by filtration, rinsed with water and dried to afford the title compound **9** (600 mg, 1.47 mmol, 93% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ(ppm) : AB system (δ_A = 7.87, δ_B = 7.41, J = 8.2 Hz, 4H), 7.68-7.58 (m, 1H), 7.12-6.56 (m, 5H), 5.75 (d, J = 5.5 Hz, 1H), 4.53 (d, J = 6.3 Hz, 2H), 3.74 and 3.72 (2s, 6H), 3.48-3.30 (m, 2H), 2.80-2.60 (m, 2H).

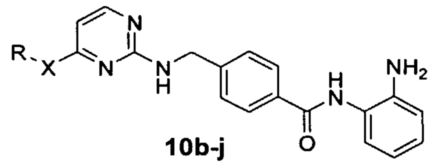
[0292] Step 4: N-(2-Amino-phenyl)-4-({4-[2-(3,4-dimethoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-methyl)-benzamide (10a)

[0293] To a stirred solution of **9a** (300 mg, 0.73 mmol) in anhydrous DMF (10 mL) at room temperature under nitrogen were added Et_3N (123 μl, 0.88 mmol) and BOP reagent (358 mg, 0.81 mmol), respectively. After 30 min, a solution of 1,2-phenylenediamine (95 mg, 0.88 mmol), Et_3N (307 μl, 2.20 mmol) in anhydrous DMF (2 mL) was added drop wise. After stirring overnight, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, and extracted with AcOEt. The organic layer was successively washed with saturated NH_4Cl, water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 5/95 →10/90 plus a few drops of NH_4OH) and co-precipitated in a mixture of AcOEt/MeOH/hexane to afford the title compound **10a** (280 mg, 0.56 mmol, 76% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.60 (s, 1H), AB system (δ_A = 7.91, δ_B = 7.43, J = 8.0 Hz, 4H), 7.71-7.58 (m, 1H), 7.17 (d, J = 7.4 Hz, 1H), 7.20-7.00 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.84-6.64 (m, 3H), 6.61 (t, J = 7.4 Hz, 1H), 5.76 (d, J = 5.3 Hz, 1H), 4.90 (bs, 2H), 4.54 (d, J = 6.1 Hz, 2H), 3.74 (s, 6H), 3.50-3.35 (m, 2H), 2.80-2.62 (m, 2H).

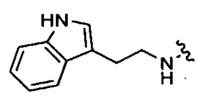
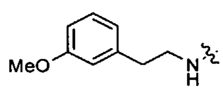
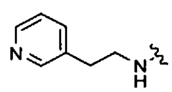
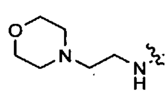
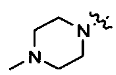
Examples 3-11:

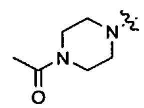
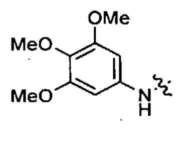
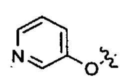
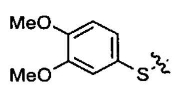
[0294] **Examples 3-11** (compounds **10b**-**10j**) were prepared using the same procedures as described for the compound **10a**, example 2 (scheme 2).

Table 1

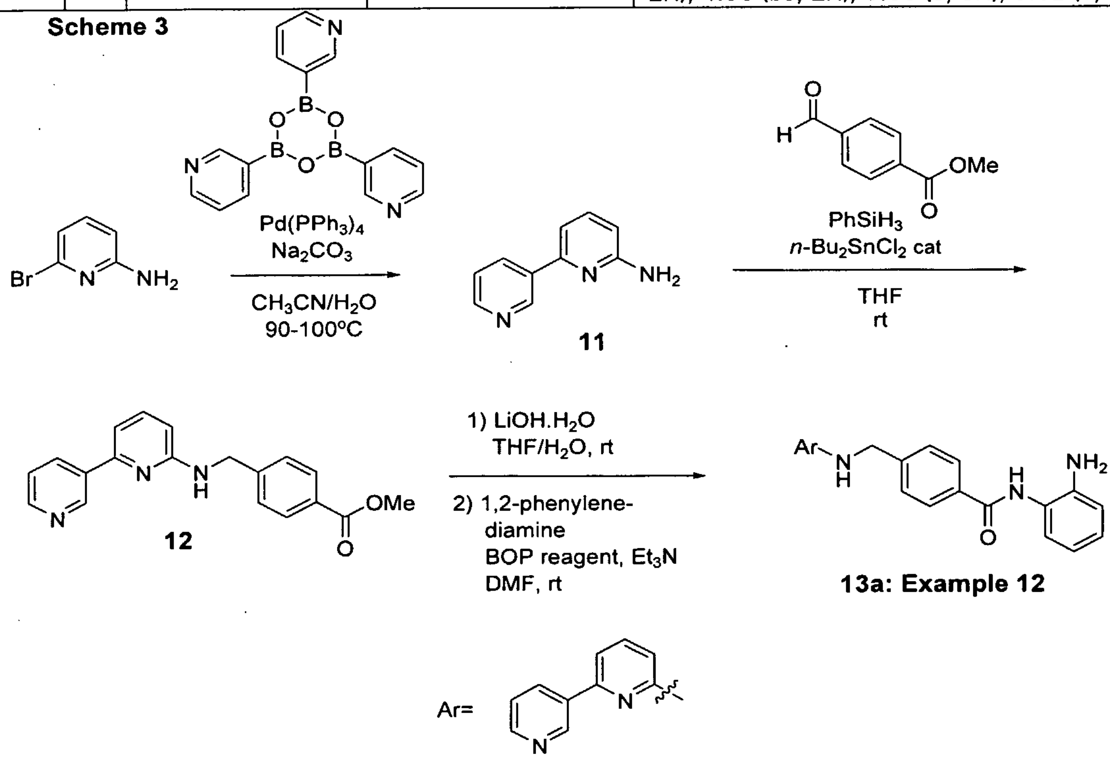


10b-j

Cmpd	Ex	R-X	Name	Characterization
10b	**3**		*N*-(2-Amino-phenyl)-4-({4-[2-(1*H*-indol-3-yl)-ethylamino]-pyrimidin-2-ylamino}-methyl)-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 10.82 (s, 1H), 9.60 (s, 1H), AB system (δ_A = 7.90, δ_B = 7.43, J_{AB} = 8.1 Hz, 4H), 7.64 (bs, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.25-6.90 (m, 7H), 6.79 (dd, J = 8.0, 1.4 Hz, 1H), 6.61 (td, J = 7.5, 1.4 Hz, 1H), 5.76 (d, J = 5.1 Hz, 1H), 4.90 (s, 2H), 4.54 (d, J = 6.1 Hz, 2H), 3.63-3.43 (m, 2H), 2.93 (t, J = 7.3 Hz, 2H).
10c	**4**		*N*-(2-Amino-phenyl)-4-({4-[2-(3-methoxy-phenyl)-ethylamino]-pyrimidin-2-ylamino}-methyl)-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.60 (s, 1H), AB system (δ_A = 7.91, δ_B = 7.43, J = 8.2 Hz, 4H), 7.64 (bs, 1H), 7.25-6.92 (m, 5H), 6.87-6.68 (m, 4H), 6.61 (td, J = 7.5, 1.4 Hz, 1H), 5.75 (d, J = 5.3 Hz, 1H), 4.90 (bs, 2H), 4.54 (d, J = 6.3 Hz, 2H), 3.75 (s, 3H), 3.52-3.38 (m, 2H), 2.84-2.70 (m, 2H).
10d	**5**		*N*-(2-Amino-phenyl)-4-{[4-(2-pyridin-3-yl-ethylamino)-pyrimidin-2-ylamino]-methyl}-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.60 (s, 1H), 8.47-8.33 (m, 2H), AB system (δ_A = 7.91, δ_B = 7.42, J = 8.0 Hz, 4H), 7.70-7.50 (m, 2H), 7.36-7.28 (m, 1H), 7.25-7.03 (m, 2H), 7.17 (d, J = 7.4 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.61 (t, J = 7.5 Hz, 1H), 5.75 (d, J = 5.9 Hz, 1H), 4.90 (bs, 2H), 4.53 (d, J = 6.1 Hz, 2H), 3.53-3.39 (m, 2H), 2.88-2.73 (m, 2H).
10e	**6**		*N*-(2-Amino-phenyl)-4-{[4-(2-morpholin-4-yl-ethylamino)-pyrimidin-2-ylamino]-methyl}-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.61 (s, 1H), AB system (δ_A = 7.91, δ_B = 7.41, J = 8.0 Hz, 4H), 7.68-7.57 (m, 1H), 7.25-6.85 (m, 2H), 7.16 (d, J = 7.4 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.61 (t, J = 7.3 Hz, 1H), 5.77 (d, J = 5.5 Hz, 1H), 4.90 (bs, 2H), 4.51 (d, J = 6.3 Hz, 2H), 3.66-3.50 (m, 4H), 3.40-3.26 (m, 2H), 2.50-2.24 (m, 6H).
10f	**7**		*N*-(2-Amino-phenyl)-4-{[4-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-methyl}-benzamide	^{1}H NMR (400 MHz, CD_3OD) δ(ppm) : 7.90 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 5.9 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 7.16 (m, 1H), 7.06 (m, 1H), 6.89 (m, 1H), 6.75 (m, 1H), 6.05 (d, J = 6.7 Hz, 1H), 4.58 (s, 2H), 3.60 (m, 4H), 2.42 (m, 4H), 2.18 (s, 3H).

Cmpd	Ex	R-X	Name	Characterization
10g	**8**		4-{[4-(4-Acetyl-piperazin-1-yl)-pyrimidin-2-ylamino]-methyl}-*N*-(2-amino-phenyl)-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.78 (s, 1H), 8.71 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.89 (d, J = 7.0 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 7.8 Hz, 1H), 7.0 (dd, J = 7.8, 7.4 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.70 (m, 1H), 6.51 (d, J = 7.0 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 3.76 (m, 4H), 3.34 (m, 6H), 2.03 (s, 3H).
10h	**9**		*N*-(2-Amino-phenyl)-4-{[4-(3,4,5-trimethoxy-phenylamino)-pyrimidin-2-ylamino]-methyl}-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.50 (s, 1H), 9.07 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 5.7 Hz, 1H), 7.31(d, J = 8.0 Hz, 3H), 7.05 (d, J = 6.7 Hz, 1H), 6.96 (s, 2H), 6.87 (m, 1H), 6.68 (m, 1H), 6.50 (m, 1H), 5.93 (d, J = 5.7 Hz, 1H), 4.82 (bs, 2H), 4.54 (bs, 2H), 3.75-3.40 (m, 9H).
10i	**10**		*N*-(2-Amino-phenyl)-4-{[4-(pyridin-3-yloxy)-pyrimidin-2-ylamino]-methyl}-benzamide	^{1}H NMR (500 MHz, DMSO-d_6) δ(ppm) : 9.58 (s, 1H), 8.49 (bs, 1H), 8.20 (m, 1H), 8.03 (bs, 1H), 7.81 (m, 3H), 7.59 (bs, 1H), 7.50 (bs, 1H), 7.36 (bs, 1H), 7.14 (m, 1H), 7.04 (bs, 1H), 6.96 (m, 1H), 6.76 (m, 1H), 6.59 (m, 1H), 6.28 (bs, 2H), 4.87 (s, 2H), 4.49 (s, 1H), 4.16 (s, 1H).
10j	**11**		*N*-(2-Amino-phenyl)-4-{[4-(3,4-dimethoxy-phenylsulfanyl)-pyrimidin-2-ylamino]-methyl}-benzamide	^{1}H NMR (300 MHz, DMSO-d_6) δ(ppm) : 9.64 (s, 1H), 8.03 (d, J = 5.3 Hz, 1H), 7.94 (m, 3H), 7.39 (bs, 2H), 7.19 (m, 4H), 7.02 (dd, J = 7.5, 7.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.66 (dd, J = 7.5, 7.5 Hz, 1H), 6.04 (bs, 1H), 4.93 (s, 2H), 4.53 (bs, 2H), 3.88 (s, 3H), 3.82 (s, 3H).

Scheme 3



Example 12:

N-(2-Amino-phenyl)-4-([2,3']bipyridinyl-6-ylaminomethyl)-benzamide (13a)

[0295] Step 1: [2,3']Bipyridinyl-6-ylamine (11)

[0296] To a stirred degassed suspension of a mixture of 2-amino-6-bromopyridine (5.38 g, 31.09 mmol), 2,4,6-(3-pyridinyl)-cyclotriboroxane (3.80 g, 12.07 mmol) and aqueous Na_2CO_3 (100 mL, 0.4M) in acetonitrile (100 mL) at room temperature $Pd(PPh_3)_4$ (1.70 g, 1.47 mmol) was added. The reaction mixture was heated at 95□for 1 to 2 days under nitrogen, cooled to the room temperature and filtered. The filtrate was concentrated purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 5/95→10/90 plus a few drops of NH_4OH) and co-precipitated with a mixture of $AcOEt/CH_2Cl_2$/hexane to afford the title compound **11** (4.091 g, 23.90 mmol, 77% yield) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.16 (dd, J = 2.2, 0.8 Hz, 1H), 8.57 (dd, J = 4.7, 1.6 Hz 1H), 8.33-8.28 (m, 1H), 7.54-7.44 (m, 2H), 7.14 (dd, J = 7.3, 0.5 Hz, 1H), 6.49 (dd, J = 8.2, 0.4 Hz 1H), 6.12 (bs, 2H).

[0297] Step 2: Methyl 4-([2,3']bipyridinyl-6-ylaminomethyl)-benzoate (12)

[0298] To a stirred suspension of a mixture of **11** (3.00 g, 17.52 mmol), methyl 4-formylbenzoate (4.62 g, 28.11 mmol, 1.5-2.0 equiv.) and dibutyl tin dichloride 160 mg, 0.53 mmol) in anhydrous THF (15 mL) at room temperature was added phenylsilane (2.34 mL, 19.28 mmol) in three portions over two days. After stirring for 2 to 7 days the reaction mixture was filtered, filtrate was concentrated and purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$, 2/98→10/90) to afford the title compound **12** (5.50 g, 17.22 mmol, 98% yield) as a pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.11 (dd, J = 2.3, 0.7 Hz, 1H), 8.55 (dd, J = 4.7, 1.8 Hz 1H), 8.29-8.24 (m, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.57-7.40 (m, 5H), 7.18 (d, J = 7.2 Hz, 1H), 6.59 (d, J = 8.2 Hz 1H), 4.69 (d, J = 6.1 Hz, 2H), 3.85 (s, 3H).

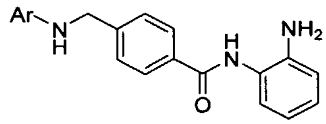
[0299] Step 3: N-(2-Amino-phenyl)-4-([2,3']bipyridinyl-6-ylaminomethyl)-benzamide (13a)

[0300] The title compound **13a** (Example 12) was obtained from **12** as an off-white solid in two steps following the same procedure as in Example 2, steps 3 and 4 (Scheme 2). ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.60 (s, 1H), 9.16 (dd, J = 2.2, 0.9 Hz, 1H), 8.56 (dd, J = 4.8, 1.7 Hz 1H), 8.31 (ddd, J = 7.8, 2.3, 1.7 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.57-7.48 (m, 3H), 7.46 (ddd, J = 8.0, 4.7, 0.8 Hz, 1H), 7.42 (t, J = 6.1 Hz, 1H), 7.19 (dd, J = 7.2, 0.6 Hz, 1H), 7.17 (dd, J = 7.3, 1.0 Hz, 1H), 6.98 (td, J = 7.5, 1.4, 1H), 6.79 (dd, J = 7.8, 1.4 Hz 1H), 6.65-6.57 (m, 2H), 4.90 (bs, 2H), 4.69 (d, J = 6.1 Hz, 2H).

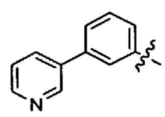
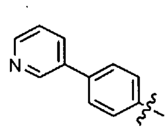
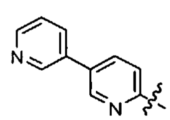
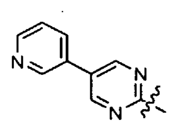
Examples 13-16:

[0301] **Examples 13-16** (compounds **13b-13e**) were prepared using the same procedures as described for compound **13a**, example 12 (scheme 3).

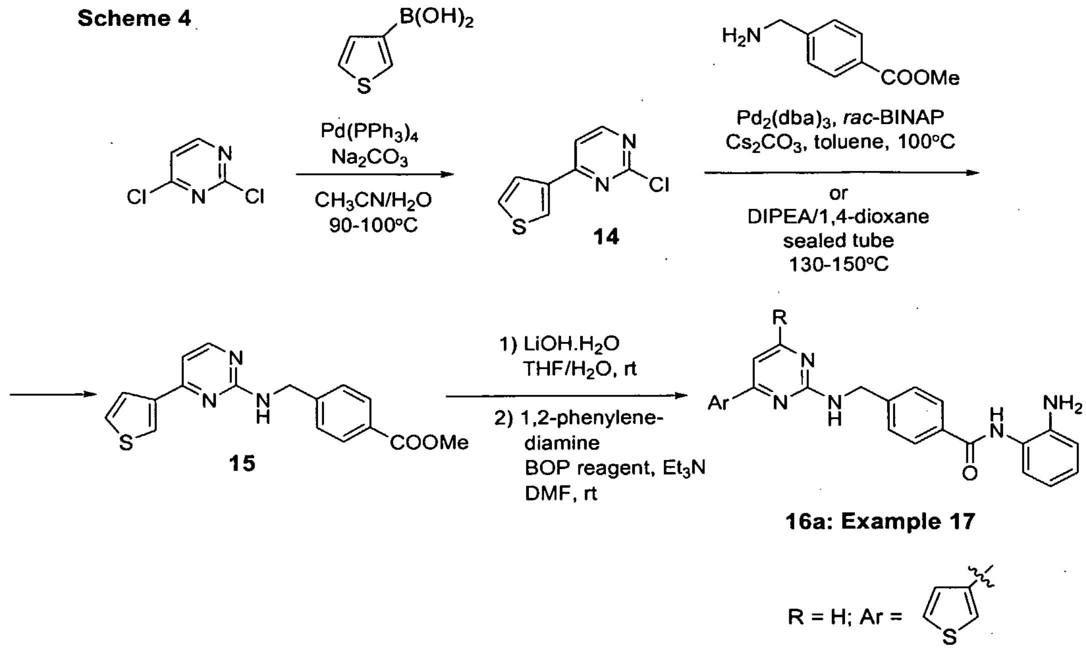
Table 2



13b-e

Cmpd	Ex	Ar	Name	Characterization
13b	**13**		*N*-(2-Amino-phenyl)-4-[(3-pyridin-3-yl-phenylamino)-methyl]-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.57 (s, 1H), 8.73 (dd, J = 2.6, 1.0 Hz, 2H), 8.50 (dd, J = 4.8, 1.6 Hz, 1H), 7.93-7.88 (m, 3H), 7.49 (d, J = 8.4 Hz, 2H), 7.42 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H), 7.14 (q, J = 7.6 Hz, 2H), 6.93 (td, J = 8.0, 1.6 Hz, 1H), 6.86-6.81 (m, 2H), 6.74 (dd, J = 8.0, 1.2 Hz, 1H), 6.63-6.52 (m, 3H), 4.86 (s, 2H), 4.43 (d, J = 6.0 Hz, 2H).
13c	**14**		*N*-(2-Amino-phenyl)-4-[(4-pyridin-3-yl-phenylamino)-methyl]-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.58 (s, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.38 (dd, J = 4.4, 1.2 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.90-7.86 (m, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.34 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H), 7.12 (d, J = 8.0, 1.2 Hz, 1H), 6.94 (td, J = 7.6, 1.6 Hz, 1H), 6.75 (dd, J = 8.0, 1.2 Hz, 1H), 6.70-6.63 (m, 3H), 6.56 (td, J = 7.6, 1.6 Hz, 1H), 4.87 (s, 2H), 4.41 (d, J = 6.4 Hz, 2H).
13d	**15**		*N*-(2-Amino-phenyl)-4-([3,3']bipyridinyl-6-ylaminomethyl)-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.62 (s, 1H), 8.83 (dd, J = 2.4, 0.7 Hz, 1H), 8.48 (dd, J = 4.7, 1.6 Hz 1H), 8.38 (d, J = 2.5 Hz, 1H), 7.99 (ddd, J = 7.9, 2.3, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 8.8, 2.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.43 (ddd, J = 7.9, 4.7, 0.7 Hz, 1H), 7.18 (d, J = 7.0 Hz, 1H), 6.99 (td, J = 7.6, 1.6, 1H), 6.79 (dd, J = 8.0, 1.4 Hz 1H), 6.68 (d, J = 8.6 Hz, 1H), 6.61 (td, J = 7.5, 1.3 Hz, 1H), 4.91 (bs, 2H), 4.65 (d, J = 6.1 Hz, 2H).
13e	**16**		*N*-(2-Amino-phenyl)-4-[(5-pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.62 (s, 1H), 8.88 (d, *J* = 2.2 Hz, 1H), 8.72 (bs, 2H), 8.54 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.15 (t, *J* = 6.5 Hz, 1H), 8.06 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.48-7.45 (m, 3H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.98 (td, *J* = 7.6, 1.3 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.61 (td, *J* = 7.7, 1.2 Hz, 1H), 4.91 (s, 2H), 4.66 (d, *J* = 6.3 Hz, 2H).

Scheme 4



Example 17:

_N_-(2-Amino-phenyl)-4-[(4-thiophen-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide. (16a)

[0302] Step 1: 2-Chloro-4-thiophen-3-yl-pyrimidine (14)

[0303] To a solution of 3-thiopheneboronic acid (500 mg, 3.91 mmol) and 2,4-dichloropyrimidine (1.16 g, 7.81 mmol) in acetonitrile (20 mL) was added a 0.4 M solution of Na_2CO_3 (20 mL) followed by $Pd(PPh_3)_4$ (450 mg, 0.39 mmol). The suspension was degassed and heated at 90°C for 16 h under nitrogen, cooled down, concentrated and extracted with EtOAc. Organic layer was successively washed with saturated solution of NH_4Cl, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/CH_2Cl_2: 2/98) to afford the title compound **14** (680 mg, 3.46 mmol, 88% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ (ppm) : 8.56 (d, J = 5.2 Hz, 1H), 8.19 (dd, J = 3.2, 1.2 Hz, 1H), 7.66 (dd, J = 5.2, 1.2 Hz, 1H), 7.46 (d, J = 5.2 Hz, 1H), 7.43 (dd, J = 5.2, 2.8 Hz, 1H).

[0304] Step 2: Methyl 4-[(4-thiophen-3-yl-pyrimidin-2-ylamino)-methyl]-benzoate (15)

[0305] To a solution of **14** (680 mg, 3.46 mmol) and methyl 4-(aminomethyl)benzoate (686 mg, 4.51 mmol) in dry 1,4-dioxane (10 mL) was added DIPEA (1.50 mL, 8.65 mmol) and the mixture was heated for 48 h at 130°C in a sealed tube. Solvents were removed under vacuum and the residue was triturated with a mixture of EtOAc/Et_2O, to form a solid, which was collected by filtration and dried. This material was purified by flash chromatography on silica gel (EtOAc/CH_2Cl_2 : 30/70) to afford the title compound **15** (540 mg, 1.66 mmol, 48% yield). ^{1}H NMR: (400 MHz, DMSO-d_6) δ (ppm) : 8.29-8.23 (m, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.84-7.77 (m,

1H), 7.69-7.59 (m, 2H), 7.52-7.43 (m, 2H), 7.03 (d, J = 5.2 Hz, 1H), 4.60 (d, J = 6.4 Hz, 2H), 3.81 (s, 3H).

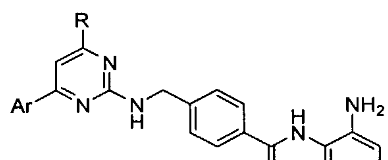
[0306] Steps 3: N-(2-Amino-phenyl)-4-[(4-thiophen-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide (16a)

[0307] The title compound **16a** (example 17) was obtained from **15** as an off-white solid in two steps following the same procedure as in Example 2, steps 3 and 4 (Scheme 2). ^{1}H NMR: (400 MHz, DMSO-d_6) δ (ppm): 9.59 (s, 1H), 8.32-8.27 (m, 2H), 7.91 (d, J = 8.0 Hz, 2H), 7.83 (t, J = 6.4 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 7.68-7.63 (m, 1H), 7.54-7.44 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 5.2 Hz, 1H), 6.96 (td, J = 7.6, 1.6 Hz, 1H), 6.77 (dd, J = 8.0, 1.2 Hz, 1H), 6.59 (td, J = 7.6, 1.2 Hz, 1H), 4.89 (s, 2H), 4.62 (d, J = 6.4 Hz, 2H).

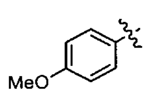
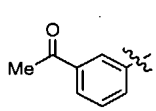
Examples 18-24:

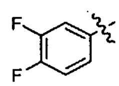
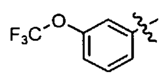
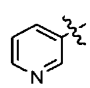
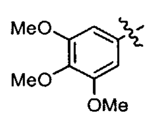
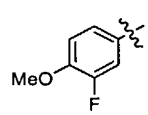
[0308] **Examples 18-24** (compounds **16b-16h**) were prepared using the same procedure as described for compound **16a**, example 17, (scheme 4).

Table 3

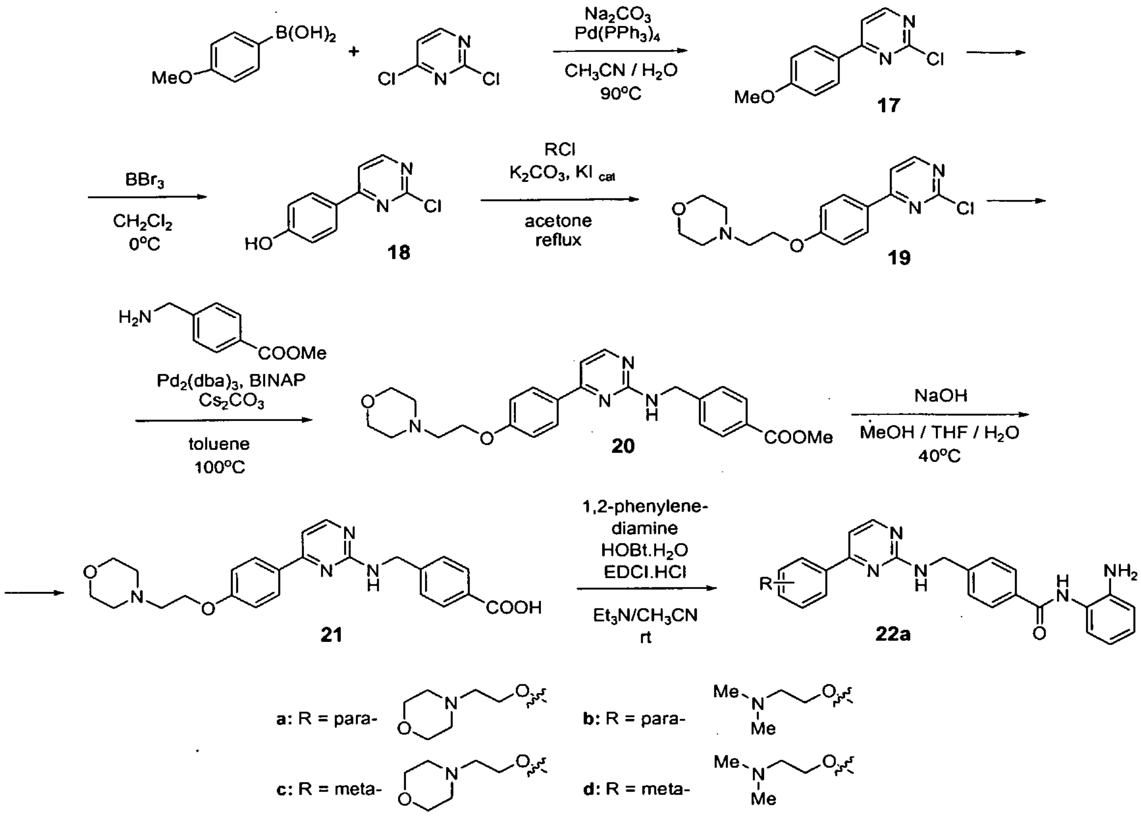


16b-h

Cmpd	Ex.	Ar	R	Name	Characterization
16b	**18**	 MeO	**H**	N-(2-Amino-phenyl)-4-{[4-(4-methoxy-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 9.56 (s, 1H), 8.26 (d, J = 5.2, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.79 (t, J = 6.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 7.2 Hz, 1H), 7.09 (d, J = 5.2 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.55 (td, J = 7.2, 1.2 Hz, 1H), 6.74 (dd, J = 8.0, 1.2 Hz, 1H), 6.56 (t, J = 7.6 Hz, 1H), 4.86 (s, 2H), 4.62 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H).
16c	**19**	 O Me	**H**	4-{[4-(3-Acetyl-phenyl)-pyrimidin-2-ylamino]-methyl}-N-(2-amino-phenyl)-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 9.55 (s, 1H), 8.58 (s, 1H), 8.36 (d, J = 4.8 Hz, 1H), 8.28 (d, J = 7.2 Hz, 1H), 8.10-7.98 (m, 1H), 8.00 (t, J = 6.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.47 (bs, 2H), 7.24 (d, J = 5.2 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.92 (td, J = 7.6, 1.6 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.54 (t, J = 7.6 Hz, 1H), 4.85 (s, 2H), 4.61 (d, J = 6.0 Hz, 2H), 2.63 (s, 3H).

Cmpd	Ex.	Ar	R	Name	Characterization
16d	**20**		**H**	*N*-(2-Amino-phenyl)-4-{[4-(3,4-difluoro-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide	[1]H NMR (400 MHz, DMSO-d_6) δ (ppm) : 9.55 (s, 1H), 8.35 (d, J = 5.2, 1H), 8.14-8.04 (m, 1H), 7.99-7.91 (m, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.60-7.38 (m, 3H), 7.19 (d, J = 5.2 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.92 (td, J = 7.6, 1.6 Hz, 1H), 6.73 (dd, J = 7.6, 1.6 Hz, 1H), 6.55 (t, J = 6.8 Hz, 1H), 4.85 (m, 1H), 4.61 (d, J = 4.8 Hz, 2H).
16e	**21**		**H**	*N*-(2-Amino-phenyl)-4-{[4-(3-trifluoromethoxy-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide	[1]H NMR (400 MHz, DMSO-d_6) δ (ppm) : 9.56 (s, 1H), 8.37 (d, J = 5.2, 1H), 8.12-7.95 (m, 3H), 7.88 (d, J = 8.0 Hz, 2H), 7.65-7.57 (m, 1H), 7.53-7.40 (m, 3H), 7.22 (d, J = 5.2 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.92 (td, J = 7.6, 1.2 Hz, 1H), 6.73 (dd, J = 8.0, 1.2 Hz, 1H), 6.55 (t, J = 7.2 Hz, 1H), 4.84 (m, 2H), 4.60 (d, J = 6.4 Hz, 2H).
16f	**22**		**NH_2**	*N*-(2-Amino-phenyl)-4-[(4-amino-6-pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide	[1]H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.60 (s, 1H), 9.06 (d, J = 1.6 Hz, 1H), 8.62 (d, J = 3.7 Hz, 1H), 8.22 (bd, J = 7.8 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.56-7.44 (m, 3H), 7.35-7.15 (m, 1H), 7.17 (d, J = 7.4 Hz, 1H), 6.98 (td, J = 7.6, 1.5 Hz, 1H), 6.78 (dd, J = 8.0, 1.4 Hz, 1H), 6.61 (t, J = 7.4 Hz, 1H), 6.65-6.45 (m, 2H), 6.30 (s, 1H), 5.04-4.80 (m, 2H), 4.62 (d, J = 6.3 Hz, 2H).
16g	**23**		**H**	*N*-(2-Amino-phenyl)-4-{[4-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide	[1]H NMR (300 MHz, DMSO-d_6) δ (ppm) : 9.64 (s, 1H), 8.40 (d, J = 5.3 Hz, 1H), 7.97 (d, J = 7.9 Hz, 3H), 7.56(d, J = 7.5 Hz, 2H), 7.41 (s, 2H), 7.28 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 7.9, 7.0 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.64 (dd, J = 7.5, 7.5 Hz, 1H), 4.92 (s, 2H), 4.67 (d, J = 6.2 Hz, 2H), 3.90 (s, 3H), 3.77 (s, 3H).
16h	**24**		**H**	*N*-(2-Amino-phenyl)-4-{[4-(3-fluoro-4-methoxy-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide	[1]H NMR (400 MHz, DMSO-d_6) δ (ppm) : 9.49 (s, 1H), 8.22 (d, J = 5.1 Hz, 1H), 7.80 (m, 5H), 7.39 (d, J = 6.3 Hz, 2H), 7.18 (t, J = 8.4 Hz, 1H), 7.06 (m, 2H), 6.86 (m, 1H), 6.67 (m, 1H), 6.49 (m, 1H), 4.78 (s, 2H), 4.54 (d, J = 5.9 Hz, 2H), 3.82 (s, 3H).

Scheme 5



22a: Example 25
22b: Example 26
22c: Example 27
22d: Example 28

Example 25:

N-(2-Amino-phenyl)-4-({4-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrimidin-2-ylamino}-methyl)-benzamide (22a)

[0309] Step 1: 2-Chloro-4-(4-methoxy-phenyl)-pyrimidine (17)

[0310] To a solution of 4-methoxyphenylboronic acid (3.0 g, 19.7 mmol) and 2,4-dichloropyrimidine (5.9 g, 39.0 mmol) in dry acetonitrile (120 mL) was added a 0.4 M solution of Na_2CO_3 (120 mL) followed by $Pd(PPh_3)_4$ (400 mg, 0.35 mmol). The suspension was degassed and heated at 90°C for 16 h, cooled down and concentrated to produce a precipitate which was collected by filtration, washed with water, dried and purified by flash chromatography on silica gel ($EtOAc/CH_2Cl_2$: 5/95) to afford the title compound **17** (4.25 g, 19.3 mmol, 97% yield).

[0311] Step 2: 4-(2-Chloro-pyrimidin-4-yl)-phenol (18)

[0312] To a solution of **17** (3.7 g, 16.8 mmol) in dry dichloromethane (42 mL) at 0°C was added boron tribromide (3.17 mL, 33.5 mmol). The mixture was stirred vigorously at room

temperature for 16 h, cooled down to 0°C. Ice-water was poured-in and the stirring was continued for 30 min. The reaction mixture was concentrated to form a precipitate which was collected by filtration, washed with water, dried and purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 2/98) to afford the title compound **18** (3.28 g, 15.9 mmol, 94% yield). ^1H NMR: (400 MHz, DMSO-d_6) δ (ppm) : 10.26 (s, 1H), 8.66 (d, J = 5.6 Hz, 1H), 8.05 (td, J = 8.4, 1.6 Hz, 2H), 7.96 (d, J = 5.6 Hz, 1H), 6.90 (td, J = 8.4,1.6 Hz, 2H).

[0313] Step 3: 4-{2-[4-(2-Chloro-pyrimidin-4-yl)-phenoxy]-ethyl}-morpholine (19)

[0314] To a solution of **18** (1.8 g, 8.71 mmol) in acetone (80 mL) were added 4-(2-chloroethyl)morpholine hydrochloride (1.95g, 10.5 mmol), potassium iodide (360 mg, 2.2 mmol) and potassium carbonate (6.0 g, 44.0 mmol), respectively. The reaction mixture was refluxed for 16 h and concentrated. The residue was diluted with water and the aqueous phase was extracted twice with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to form a residue was purified by flash chromatography on silica gel ($EtOAc/CH_2Cl_2$, 50/50 to $MeOH/CH_2Cl_2$: 2/98) to afford the title compound **19** (2.7 g, 8.4 mmol, 96% yield).

[0315] Step 4: Methyl 4-({4-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrimidin-2-ylamino}-methyl)-benzoate (20)

[0316] To a solution of **19** (2.7 g, 8.4 mmol) and methyl 4-(aminomethyl)benzoate hydrochloride (2.7 g, 13.5 mmol) in dry toluene (33 mL) was added cesium carbonate (8.2 g, 25.3 mmol) followed by $Pd_2(dba)_3$ (464 mg, 0.51 mmol) and *rac*-BINAP (473 mg, 0.76 mmol). The solution was degassed and heated at 100°C for 16 h. The reaction mixture was partitioned between water and EtOAc and the phases were separated. The organic layer was successively washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to form a residue which was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 2/98) to afford the title compound **20** (1.9 g, 4.2 mmol, 50% yield).

[0317] Step 5: 4-({4-[4-(2-Morpholin-4-yl-ethoxy)-phenyl]-pyrimidin-2-ylamino}-methyl)-benzoic acid (21)

[0318] To a solution of **20** (1.9 g, 4.2 mmol) in a mixture of THF (8 mL), MeOH (8 mL) and water (4 mL) was added NaOH (373 mg, 9.3 mmol). The mixture was heated at 40°C for 16 h, then acidified to pH 6 by adding 1N HCl, concentrated, and dried under high vacuum to afford the title compound **21,** which was used without further purification.

[0319] Step 6: N-(2-Amino-phenyl)-4-({4-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrimidin-2-ylamino}-methyl)-benzamide (22a)

[0320] To a solution of **21** (crude from the previous step) in dry acetonitrile (50 mL) was added 1,2-phenylenediamine (1.83 g, 16.9 mmol) followed by Et_3N (2.65 mL, 19.0 mmol), HOBt.H_2O (1.03 g, 7.6 mmol) and EDCI.HCl (1.62 g, 8.5 mmol). The mixture was stirred at room temperature for 72 h, filtered to remove salts and filtrate was concentrated to form a residue, which was purified by flash chromatography on silica gel (MeOH/CH_2Cl_2: 2/98 to 5/95). Trituration of this material with a mixture of EtOAc/CH_2Cl_2, allowed affording the title compound **22a** (696 mg, 1.3 mmol, 31% yield over 2 steps) as a white solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ (ppm) : 9.55 (s, 1H), 8.25 (d, J = 5.2 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.77 (t, J = 6.4 Hz, 1H), 7.44 (d, J = 7.2 Hz, 2H), 7.11 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 5.2 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.92 (td, J = 7.6, 1.6 Hz, 1H), 6.73 (dd, J = 8.0, 1.6 Hz, 1H), 6.55 (td, J = 7.4, 1.2 Hz, 1H), 4.85 (s, 2H), 4.61 (d, J = 5.6 Hz, 2H), 4.13 (t, J = 5.6 Hz, 2H), 3.55 (t, J = 4.4 Hz, 4H), 2.68 (t, J = 5.6 Hz, 2H), 2.45 (t, J = 4.4 Hz, 4H).

Example 26:

N-(2-Amino-phenyl)-4-({4-[3-(2-dimethylamino-ethoxy)-phenyl]-pyrimidin-2-ylamino}-methyl)-benzamide hydrochloride (22b)

[0321] The title compound **22b** was obtained in 6 steps following the same procedure as in example 25, steps 1-6 (Scheme 5) starting from 3-methoxyphenylboronic acid and using 2-(dimethylamine)ethyl chloride hydrochloride as the alkylating reagent in step 3. The compound was obtained as the hydrochloride salt by solubilizing it in a mixture of MeOH and EtOAc and by adding in a solution of 1N HCl in Et_2O. The white precipitate was filtered off, washed with EtOAc and dried under high vacuum. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.31 (d, J = 5.2 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.34-7.28 (m, 1H), 7.05 (td, J = 7.6, 1.6 Hz, 1H), 7.00-6.96 (m, 1H), 6.97 (d, J = 4.8 Hz, 1H), 6.82-6.77 (m, 2H), 6.04 (bs, 1H), 4.74 (d, J = 6.0 Hz, 2H), 4.11 (t, J = 5.2 Hz, 2H), 2.94 (t, J = 5.2 Hz, 2H), 2.45 (s, 6H).

Example 27:

N-(2-Amino-phenyl)-4-({4-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-pyrimidin-2-ylamino}-methyl)-benzamide (22c)

[0322] The title compound **22c** was obtained in 6 steps following the same procedure as in example 25 (steps 1-6, scheme 5) starting from 3-methoxyphenylboronic acid and using 4-(2-chloroethyl)morpholine hydrochloride as the alkylating reagent in step 3. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.54 (s, 1H), 8.31 (d, J = 5.2 Hz, 1H), 7.92-7.83 (m, 3H), 7.65-7.52 (m, 2H), 7.45 (d, J = 6.4 Hz, 2H), 7.35 (t, J = 8.4 Hz, 1H), 7.15 (d, J = 5.2 Hz, 1H), 7.11 (d, J = 6.8 Hz,

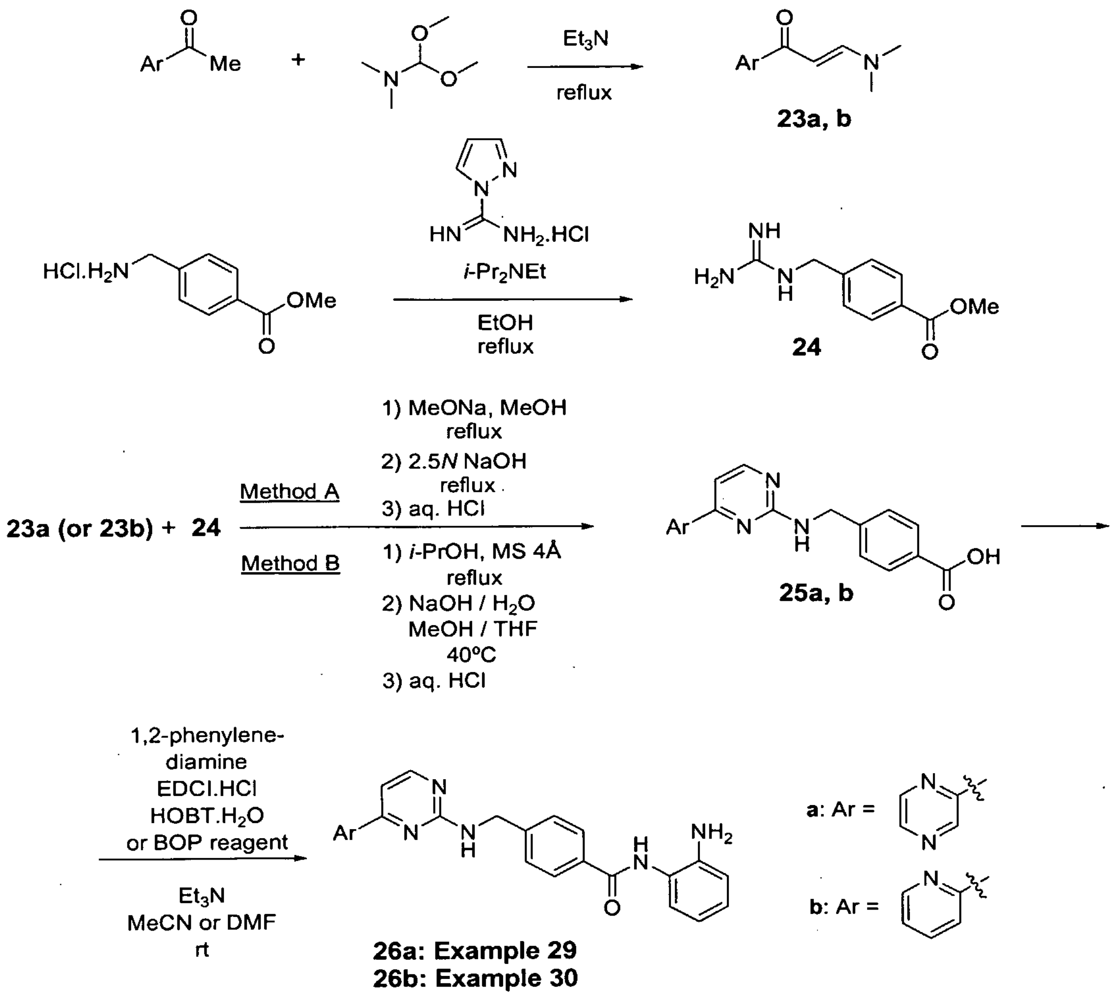
1H), 7.03 (d, J = 6.8 Hz, 1H), 6.92 (td, J = 7.6, 1.2 Hz, 1H), 6.73 (dd, J = 7.6, 1.2 Hz, 1H), 6.55 (t, J = 6.8 Hz, 1H), 4.85 (s, 2H), 4.61 (d, J = 6.0 Hz, 2H), 4.14-4.06 (m, 2H), 3.55 (t, J = 4.8 Hz, 4H), 2.70 (t, J = 5.6 Hz, 2H), 2.50-2.44 (m, 4H).

Example 28:

***N*-(2-Amino-phenyl)-4-({4-[4-(2-dimethylamino-ethoxy)-phenyl]-pyrimidin-2-ylamino}-methyl)-benzamide (22d)**

[0323] The title compound **22d** was obtained in 6 steps following the same procedure as in example 25, (steps 1-6, scheme 5) starting from 4-methoxyphenylboronic acid and using 2-(dimethylamine)ethyl chloride hydrochloride as the alkylating reagent in step 3. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.52-10.35 (bs, 1H), 9.97 (s, 1H), 8.29 (d, J = 5.2 Hz, 1H), 8.06 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.0 Hz, 2H), 8.10-7.85 (m, 1H), 7.52-7.40 (m, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.20-7.00 (m, 5H), 6.96-6.88 (m, 1H), 4.70-4.58 (m, 2H), 4.45-4.38 (t, J = 4.8 Hz, 2H), 3.54-3.46 (m, 2H), 2.83 (s, 6H).

Scheme 6



Example 29:

N-(2-Amino-phenyl)-4-[(4-pyrazin-2-yl-pyrimidin-2-ylamino)-methyl]-benzamide (26a)

[0324] Step 1: 3-Dimethylamino-1-pyrazin-2-yl-propenone (23a)

[0325] A solution of acetylpyrazine (5 g, 40.9 mmol) in *N,N*-dimethylformamide dimethyl acetal (10.9 mL, 81.8 mmol) and Et_3N (5.7 mL) was heated at 110°C for 16 h. The heating was stopped and a precipitate was formed while it was allowed to cool down to room temperature. The suspension was diluted with *tert*-butyl methyl ether; the solid was separated by filtration and washed with *tert*-butyl methyl ether. This material was triturated with the same solvent, filtered off and dried to afford the title compound **23a** as a yellow solid (5.9 g, 33.3 mmol, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.66 (dd, J = 2.4, 1.6 Hz, 1H), 7.84 (d, J = 12.4 Hz, 1H), 6.30-6.20 (m, 1H), 3.19 (s, 3H), 2.93 (s, 3H).

[0326] Step 2: 4-guanidinomethyl-benzoic acid methyl ester dihydrate (24)

[0327] To a solution of methyl 4-(aminomethyl)benzoate hydrochloride (5 g) in dry ethanol (25 mL) was added 1*H*-pyrazole-1-carboxamidine hydrochloride (4.4 g) followed by DIPEA (13.0 mL) and the mixture was refluxed for 3 h. Ethanol was removed under vacuum. To the remaining viscous oil saturated solution of $NaHCO_3$ (50 mL) was slowly added under vigorous stirring followed by addition of 300 ml water (resultant pH 9). A white solid is formed and stirring was continued for 1h. This material was filtered off, washed with water (200 mL) and *tert*-butyl methyl ether (50 mL), and dried to give the title compound **24** as a white powder (4.7 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 7.91 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.39 (s, 2H), 3.83 (s, 3H), 3.80-2.80 [m, 4H + $2H_2O$ (determined by elemental analysis]).

[0328] Step 3, Method A: 4-[(4-Pyrazin-2-yl-pyrimidin-2-ylamino)-methyl]-benzoic acid (25a)

[0329] A suspension of **24** (6.2 g, 25.4 mmol) and **23a** (3.0 g, 16.9 mmol) in anhydrous methanol (40 mL) was stirred and heated to reflux for 10 min, then a solution of sodium methoxide 95% (3.65 g, 67.6 mmol) in methanol (40 mL) was slowly added. After refluxing for 24 h, 20 mL of 2.5N NaOH in water were added and the refluxing was maintained for additional 24 h. The mixture was allowed to cool to the room temperature methanol was removed under reduced pressure, 100 mL of water were added and the resultant mixture was extracted with AcOEt. The aqueous phase was separated and acidified to pH 5-6 with 2N HCl to form a precipitate which was collected by filtration, rinsed with water and dried to afford the desired carboxylic acid **25a** (4.55 g, 14.8 mmol, 87%) as a white solid.

[0330] Step 4: N-(2-Amino-phenyl)-4-[(4-pyrazin-2-yl-pyrimidin-2-ylamino)-methyl]-benzamide (26a)

[0331] To a solution of **25a** (1 g, 3.3 mmol) in dry acetonitrile (35 mL) was added 1,2-phenylenediamine (0.88 g, 8.1 mmol) followed by Et_3N (2.7 mL, 19.1 mmol), HOBt.H_2O (803 mg, 5.9 mmol) and EDCI.HCl (1.89 g, 9.9 mmol). The mixture was stirred at room temperature for 16 h to form a suspension which was collected by filtration, washed successively with MeCN, water and again MeCN, triturated with MeOH, filtered and dried to afford the title compound **26a** (730 mg, 1.84 mmol, 55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.57 (s, 1H), 9.43 (s, 1H), 8.75 (d, J = 4.8 Hz, 2H), 8.49 (d, J = 5.2 Hz, 1H), 8.11 (t, J = 5.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.59-7.37 (m, 2H), 7.44 (d, J = 5.2 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.94 (td, J = 7.6, 1.6 Hz, 1H), 6.75 (dd, J = 8.0, 1.2 Hz, 1H), 6.57 (t, J = 7.2 Hz, 1H), 4.86 (s, 2H), 4.66 (d, J = 5.2 Hz, 2H).

Example 30:

***N*-(2-Amino-phenyl)-4-[(4-pyridin-2-yl-pyrimidin-2-ylamino)-methyl]-benzamide (26b)**

[0332] Compound **26b** was prepared following the same procedure as in example 29, steps 1, 2 and 4 (scheme 6). For the step 3, method B was used:

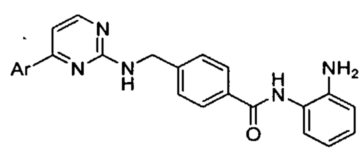
[0333] Step 3, Method B: 4-[(4-Pyridin-2-yl-pyrimidin-2-ylamino)-methyl]-benzoic acid (25b)

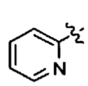
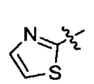
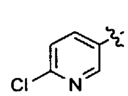
[0334] To a solution of **24** (0.85 g, 4.83 mmol) and 3-dimethylamino-1-pyridin-2-yl-propenone **23b** (1.0 g, 4.83 mmol) in *i*-PrOH (20 mL) were added molecular sieves (0.2 g, 4Å, powder, >5 μm). The reaction mixture was refluxed for 16 h then the cloudy solution was filtered through a celite pad. The mother liquor was concentrated to the half of its volume, a solid was formed which was collected by filtration and dried to give a pale yellow crystalline material (0.62 g, 1.94 mmol, 40% yield). This compound (0.456 g, 1.43 mmol) was dissolved in a mixture of THF (3 mL), MeOH (3 mL) and water (1.5 mL), then NaOH (0.125 g, 3.14 mmol) was added and the reaction mixture was stirred at 40°C for 16 h, cooled down to the room temperature, acidified to pH 5-6 by adding 1N HCl (3.2 mL), and concentrated to remove the organic solvents. A precipitate was formed which was collected by filtration, washed with water and dried afford the title compound **25b** (0.542 g, 1.37 mmol, 96% yield).

Examples 31-33:

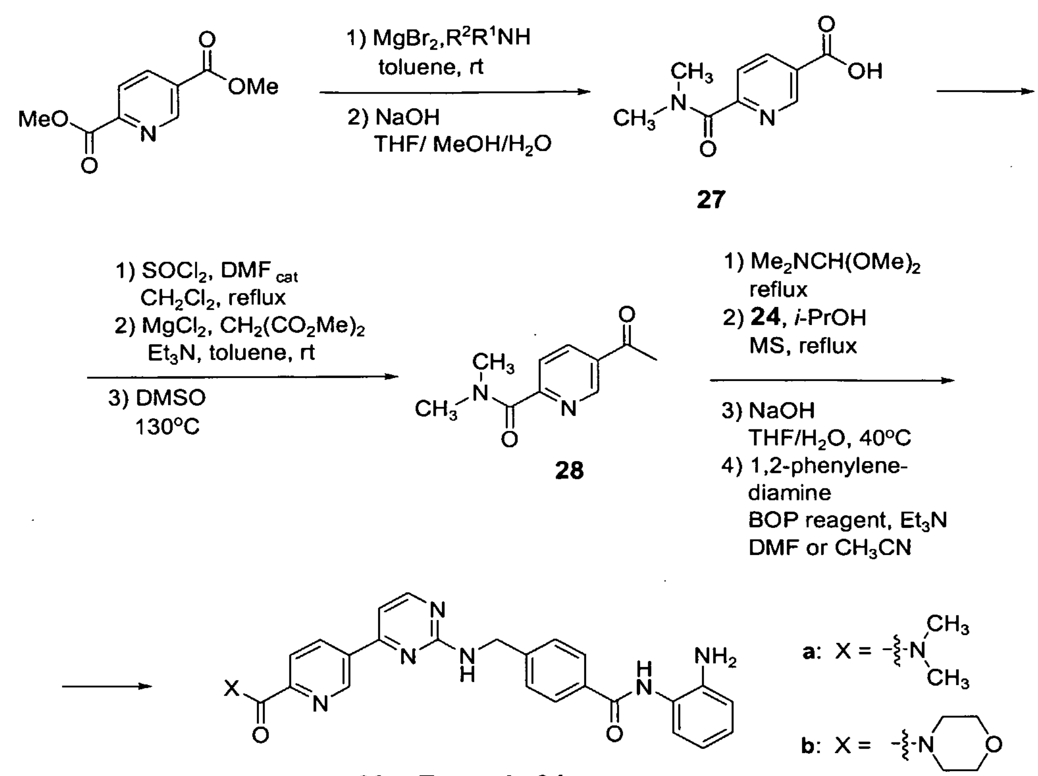
[0335] **Examples 31-33** (compounds **26b-26d**) were prepared using the same procedure as described for compound **26a** (example 29, scheme 6).

Table 4



Cmpd	Ex	Ar	Name	Characterization
26b	**31**		*N*-(2-Amino-phenyl)-4-[(4-pyridin-2-yl-pyrimidin-2-ylamino)-methyl]-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 9.55 (s, 1H), 8.65 (d, J = 4.3 Hz, 1H), 8.41 (d, J = 4.7 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.94 (m, 2H), 7.88 (d, J = 8.2 Hz, 2H), 7.46-7.50 (m, 4H), 7.11 (d, J = 7.4 Hz, 1H), 6.92 (m, 1H), 6.73 (dd, J = 7.8, 1.2 Hz, 1H), 6.55 (m, 1H), 4.84 (s, 2H), 4.64 (d, J = 5.9 Hz, 2H).
26c	**32**		*N*-(2-Amino-phenyl)-4-[(4-thiazol-2-yl-pyrimidin-2-ylamino)-methyl]-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 9.56 (s, 1H), 8.43 (d, J = 5.2, 1H), 8.18-8.08 (m, 1H), 8.02 (s, 1H), 7.95 (s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.56-7.37 (m, 2H), 7.27-7.18 (m, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.94 (td, J = 7.6, 1.6 Hz, 1H), 6.74 (dd, J = 8.0, 1.2 Hz, 1H), 6.56 (t, J = 7.2 Hz, 1H), 4.86 (s, 2H), 4.59 (d, J = 6.8 Hz, 2H).
26d	**33**		*N*-(2-Amino-phenyl)-4-{[4-(6-chloro-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 9.57 (s, 1H), 9.06 (s, 1H), 8.46 (m, 1H), 8.41 (d, J = 5.1 Hz, 1H), 8.05 (m, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.47 (m, 2H), 7.27 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 6.94 (m, 1H), 6.75 (dd, J = 8.0, 1.4 Hz, 1H), 6.57 (m, 1H), 4.87 (s, 2H), 4.64 (d, J = 6.1 Hz, 2H).

Scheme 7



29a: Example 34
29b: Example 35

<u>**Example 34:**</u>

5-{2-[4-(2-Amino-phenylcarbamoyl)-benzylamino]-pyrimidin-4-yl}-pyridine-2-carboxylic acid dimethylamide (29a)

[0336] <u>Step 1: 6-Dimethylcarbamoyl-nicotinic acid (27)</u>

[0337] To a suspension of pyridine-2,5-dicarboxylic acid dimethyl ester (10.1 g, 51.6 mmol) and $MgBr_2$ (4.75 g, 25.8 mmol) in THF (200mL) was added drop-wise a solution of dimethylamine (51.6 mL, 103.2 mmol, 2N in THF) at room temperature under nitrogen over a period of 10 min. The reaction mixture was stirred overnight and quenched with 1N HCl (52 mL) and H_2O (50mL), extracted with EtOAc (200mL x 3). The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was dissolved in a mixture of DMF (10 mL), AcOEt (50 mL), MeOH (20 mL) and DCM (50 mL), the formed solution was partially evaporated to produce a crystalline material, which was removed by filtration. The mother liquor was collected and evaporated to form a solid, which was dissolved in a mixture of THF (67 mL) and MeOH (67 mL). To this solution NaOH (2.95 g, 73.7 mmol) in H_2O (33.5 mL) was added. The reaction mixture was heated at 40□C for few hours, acidified (pH 3) to form a solid precipitate, which was

collected by filtration and dried to afford the title compound **27** (4.937g, 50% yield over two steps).

[0338] Step 2: 5-Acetyl-pyridine-2-carboxylic acid dimethylamide (28)

[0339] A suspension of **27** (4.937 g, 25.41 mmol), $SOCl_2$ (2.41 mL, 33 mmol) and DMF (0.9 mL, 5.1 mmol) in CH_2Cl_2 (51 mL) was refluxed for 3h. The reaction mixture was cooled to room temperature and evaporated to dryness. The residue was suspended in toluene and Et_3N (4.25 mL, 30.5 mmol) was added. The resulting suspension was canulated to a stirred and pre-formed suspension of dimethyl malonate (3.49 mL, 30.5 mmol), $MgCl_2$ (1.742 g, 18.3 mmol), Et_3N (10.2 mL, 73.2 mmol) in toluene (25 mL)over 2 hours. The resulting reaction mixture was stirred overnight and quenched with 1N HCl (50 mL) and water (50 mL) and extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness to give brown oil (5.21 g) which was dissolved in DMSO (15.4 mL) and H_2O (0.62 mL) and then heated at 130°C for 2 h, cooled down to room temperature, diluted with H_2O (100 mL), extracted with EtOAc. The organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (AcOEt/hexane, 70/30 to 100/0) to afford the title compound **28** (430 mg, 9% yield) as a brown crystalline solid.

[0340] Step 3: 5-{2-[4-(2-Amino-phenylcarbamoyl)-benzylamino]-pyrimidin-4-yl}-pyridine-2-carboxylic acid dimethylamide (29a)

[0341] The title compound **29a** (example 34) was obtained from **28** as an off-white solid in 4 steps following the same procedure as in example 29, steps 1, 3 (Method B) and 4 (Scheme 6). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.57 (s, 1H), 9.20 (s, 1H), 8.50 (m, 1H), 8.41 (d, J = 4.9 Hz, 1H), 8.04 (m, 1H), 7.89 (d, J = 7.8 Hz, 2H), 7.65 (m, 1H), 7.46 (m, 2H), 7.29 (d, J = 5.1 Hz, 1H), 7.11 (d, J = 7.4 Hz, 1H), 6.93 (m, 1H), 6.74 (m, 1H), 6.56 (m, 1H), 4.86 (s, 2H), 4.65 (m, 2H), 3.02 (s, 3H), 2.94 (s, 3H).

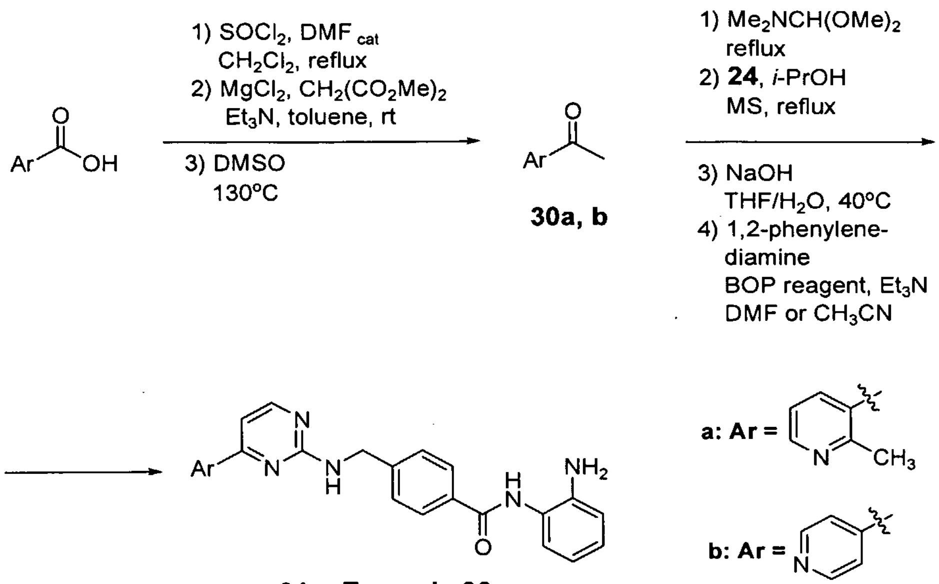
Examples 35:

N-(2-Amino-phenyl)-4-({4-[6-(morpholine-4-carbonyl)-pyridin-3-yl]-pyrimidin-2-ylamino}-methyl)-benzamide (29b)

[0342] The title compound was prepared using the same procedures as described for the compound **29a**, example 34 (scheme 7). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.55 (s, 1H), 9.21 (s, 1H), 8.52 (m, 1H), 8.42 (d, J = 4.9 Hz, 1H), 8.03 (t, J = 6.2 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.47 (m, 2H), 7.29 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 7.6 Hz,

1H), 6.93 (m, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.56 (m, 1H), 4.85 (s, 2H), 4.64 (d, J = 4.9 Hz, 2H), 3.66 (s, 4H), 3.55 (m, 2H), 3.44 (m, 2H).

Scheme 8



31a: Example 36
31b: Example 37

<u>Example 36:</u>

***N*-(2-Amino-phenyl)-4-{[4-(2-methyl-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (31a)**

[0343] <u>Step 1: 1-(2-Methyl-pyridin-3-yl)-ethanone (30a)</u>

[0344] The title compound **30a** was obtained from 2-methylnicotinic acid in 92% yield as a brown crystalline solid following the same procedure as in example 34, (step 2 scheme 7).

[0345] <u>Step2: N-(2-Amino-phenyl)-4-{[4-(2-methyl-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (31a)</u>

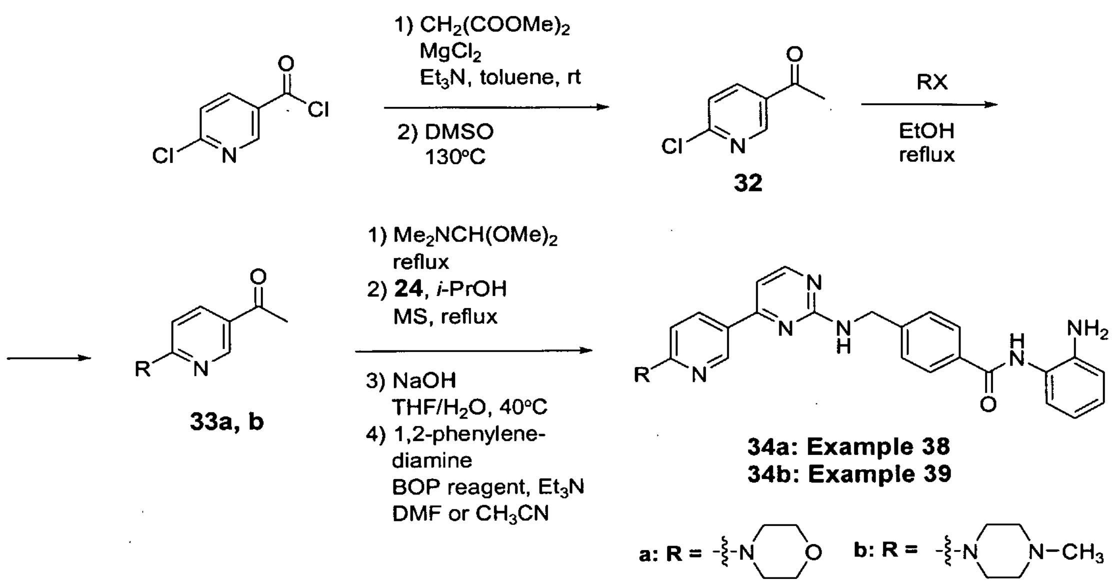
[0346] The title compound **31a** (example 36) was obtained from **30a** as an off-white solid in 4 steps following the same procedures as in example 29, steps 1, 3 (Method B) and 4 (Scheme 6). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.57 (s, 1H), 8.46 (m, 1H), 8.40 (m, 1H), 7.54 (t, J = 6.4 Hz, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 6.3 Hz, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.29 (m, 1H), 7.11 (d, J = 7.2 Hz, 1H), 6.93 (m, 1H), 6.79 (d, J = 4.9 Hz, 1H), 6.73 (dd, J = 8.0, 1.4 Hz, 1H), 6.55 (m, 1H), 4.86 (s, 2H), 4.48 (d, J = 6.3 Hz, 2H), 2.66-2.82 (m, 3H).

Example 37:

<u>***N*-(2-Amino-phenyl)-4-[(4-pyridin-4-yl-pyrimidin-2-ylamino)-methyl]-benzamide (31b)**</u>

[0347] The title compound **31b** was prepared using the same procedures as described for compound **31a** (example 36, scheme 8). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.56 (s, 1H), 8.70 (d, J = 5.3 Hz, 2H), 8.44 (d, J = 5.1 Hz, 1H), 8.05 (t, J = 6.3 Hz, 1H), 7.98 (d, J = 6.1 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H), 7.47 (bs, 2H), 7.27 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.93 (m, 1H), 6.74 (dd, J = 8.0, 1.4 Hz, 1H), 6.56 (m, 1H), 4.86 (s, 2H), 4.64 (d, J = 5.9 Hz, 2H).

Scheme 9



<u>**Example 38:**</u>

***N*-(2-Amino-phenyl)-4-{[4-(6-morpholin-4-yl-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (34a)**

[0348] <u>Step 1: 1-(6-Chloro-pyridin-3-yl)-ethanone (32)</u>

[0349] A suspension of dimethyl malonate (7.8 mL, 68.3 mmol), $MgCl_2$ (3.872 g, 40.7 mmol), Et_3N (19.1 mL, 136.9 mmol) in toluene (15 mL) at room temperature under nitrogen was stirred for 2 h. To this mixture a suspension of 6-chloro-nicotinoyl chloride (3.872 g, 40.7 mmol) and Et_3N (4.25 mL, 30.5 mmol) in toluene (46 mL) was added via canula. The resultant reaction mixture was stirred overnight, quenched with 1N HCl (100 mL) and water (100 mL) and extracted with EtOAc. The organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give white crystalline material (6.5 g) which was dissolved in a mixture DMSO (9 mL) and H_2O (0.37 mL), heated at 130°C for 5 h, cooled down to room temperature and treated with water (10 mL). A precipitate formed which was collected by filtration, rinsed with water and dried to afford the title compound **32** (1.8 g, 28% yield) as pale yellow crystalline solid.

[0350] Step 2: 1-(6-Morpholin-4-yl-pyridin-3-yl)-ethanone (33a)

[0351] A solution of **32** (1.25 g, 7.9 mmol) and morpholine (2.20 mL, 25.2 mmol) in EtOH (22 mL) was refluxed for 12 h and then evaporated to dryness. The residue was dissolved in EtOAc (200 mL), washed with saturated $NaHCO_3$ (50 mL x 2) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to afford the title compound **33a** (1.66 g, quantitative yield) as a pale yellow solid.

[0352] Step 3: N-(2-Amino-phenyl)-4-{[4-(6-morpholin-4-yl-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (34a)

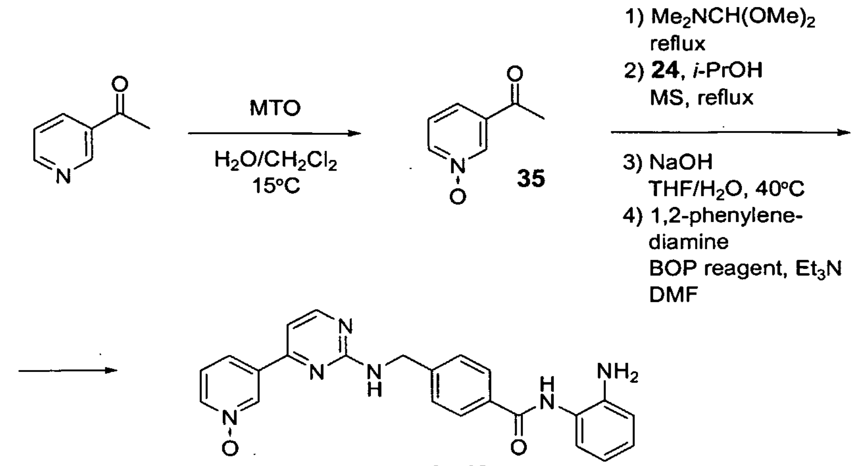
[0353] The title compound **34a** (example 38) was obtained from **33a** as off-white solid in 4 steps following the same procedure as in example 29, steps 1, 3 (Method B) and 4 (scheme 6). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.57 (s, 1H), 8.84 (s, 1H), 8.24 (d, J = 5.3 Hz, 1H), 8.18 (m, 1H), 7.90 (d, J = 7.3 Hz, 2H), 7.78 (m, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.13 (m, 1H), 7.08 (d, J = 5.3 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.91 (m, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.57 (dd, J = 7.2, 7.6 Hz, 1H), 4.87 (s, 2H), 4.61 (d, J = 6.1 Hz, 2H), 3.70 (m, 4H), 3.56 (m, 4H).

Example 39:

_N_-(2-Amino-phenyl)-4-({4-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-pyrimidin-2-ylamino}-methyl)-benzamide (34b)

[0354] Title compound **34b** was prepared using the same procedure as described for compound **34a** (example 38, scheme 9). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.55 (s, 1H), 8.81 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 8.14 (t, J = 8.6 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.75 (t, J = 6.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.4 Hz, 1H), 7.05 (d, J = 5.3 Hz, 1H), 6.93 (m, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.74 (dd, J = 8.0, 1.4 Hz, 1H), 6.56 (m, 1H), 4.87 (s, 2H), 4.62 (d, J = 6.5 Hz, 2H), 3.59 (m, 4H), 2.38 (m, 4H), 2.21 (s, 3H).

Scheme 10



36: Example 40

Example 40:

N-(2-Amino-phenyl)-4-{[4-(1-oxy-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (36)

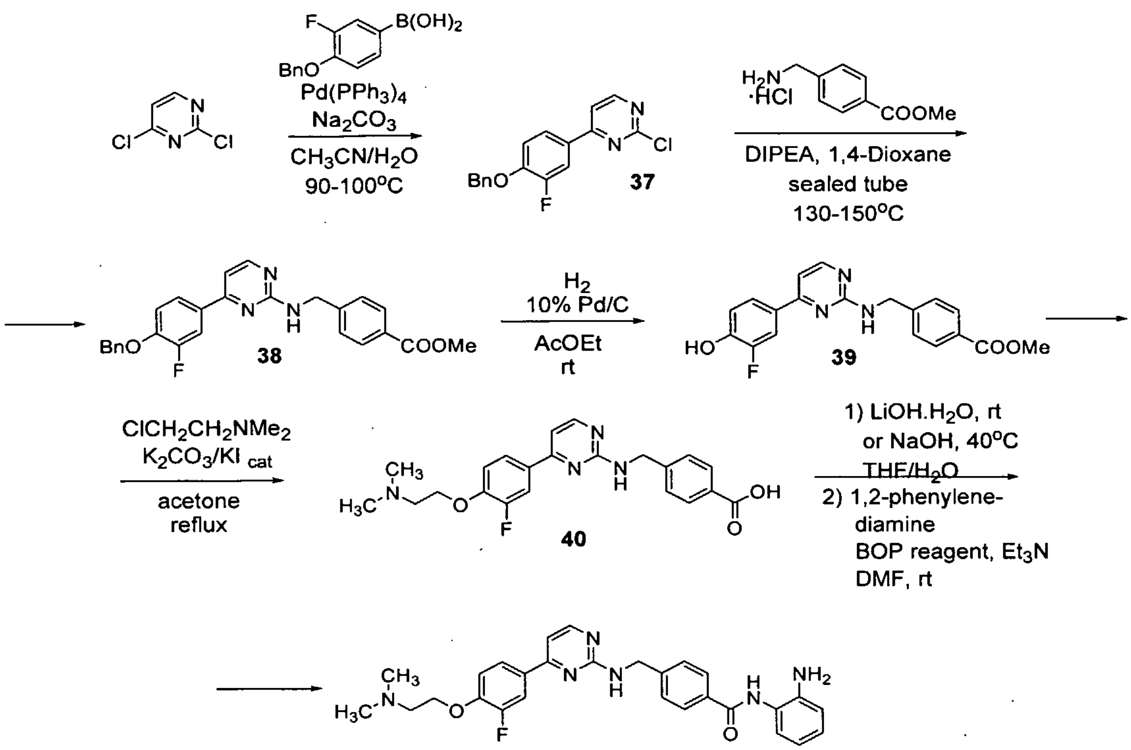
[0355] Step1: 1-(1-Oxy-pyridin-3-yl)-ethanone (35)

[0356] To a solution of 1-pyridin-3-yl-ethanone (1.00 g, 8.3 mmol) in CH_2Cl_2 (8.3 mL) at room temperature was added MTO (methyltrioxorhenium, 113 mg, 0.45 mmol) and the reaction mixture was cooled to 15°C. Aqueous solution of H_2O_2 (30%, 1.13 mL, 9.96 mmol) was added drop wise over a period of 20 min and the reaction mixture was stirred for 5 h at 15°C and cooled to 0°C. Aqueous solution of $Na_2S_2O_3$ (20%, 20 mL) was added, the mixture was stirred for 10 min, extracted with EtOAc. The aqueous layer was collected and freeze-dried to form a solid material, which was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$, 10/90) to afford the title compound **35** (1.3 g, quantitative yield).

[0357] Step 2: N-(2-Amino-phenyl)-4-{[4-(1-oxy-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (36)

[0358] The title compound **36** (example 40) was obtained from **35** as a pale yellow solid in 4 steps following the same procedure as in example 29, steps 1, 3 (Method B) and 4 (scheme 6). ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.61 (s, 1H), 8.81 (bs, 1H), 8.45 (m, 1H), 8.33 (d, J = 5.1 Hz, 1H), 8.12 (bs, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 7.0 Hz, 1H), 7.50 (m, 2H), 7.29 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 6.97 (m, 1H), 6.78 (dd, J = 8.0, 1.2 Hz, 1H), 6.60 (m, 1H), 4.91 (s, 2H), 4.67 (d, J = 6.3 Hz, 2H).

Scheme 11



41: Example 41

Example 41:

N-(2-Amino-phenyl)-4-({4-[4-(2-dimethylamino-ethoxy)-3-fluoro-phenyl]-pyrimidin-2-ylamino}-methyl)-benzamide (41)

[0359] Step 1: 4-(4-Benzyloxy-3-fluoro-phenyl)-2-chloro-pyrimidine (37)

[0360] The title compound **37** was obtained following the same procedure as in Example 25, step 1 (Scheme 5) starting with 4-benzyloxy-3-fluorobenzeneboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (d, J = 5.2 Hz, 1H), 7.90 (dd, J = 12.0, 2.4 Hz, 1H), 7.84-7.80 (m, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.48-7.32 (m, 5H), 7.10 (t, J = 8.4 Hz, 1H), 5.24 (s, 2H).

[0361] Step 2: 4-{[4-(4-Benzyloxy-3-fluoro-phenyl)-pyrimidin-2-ylamino]-methyl}-benzoic acid methyl **ester (38)**

[0362] The title compound **38** was obtained from **37** following the same procedure as in example 17 (step 2, scheme 4). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.23 (d, J = 4.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.78 (dd, J = 12.4, 2.0 Hz, 1H), 7.67 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 7.47-7.29 (m, 7H), 7.01 (t, J = 8.4 Hz, 1H), 6.88 (d, J = 5.6 Hz, 1H), 6.06-5.95 (m, 1H), 5.18 (s, 2H), 4.75 (d, J = 6.4 Hz, 2H), 3.90 (s, 3H).

[0363] Step 3: Methyl 4-{[4-(3-fluoro-4-hydroxy-phenyl)-pyrimidin-2-ylamino]-methyl}-benzoate (39)

[0364] To a degassed solution of **38** (950 mg, 2.14 mmol) in EtOAc (100 mL) at room temperature under N_2 was added 10% Pd/C (220 mg, 0.21 mmol). The mixture was hydrogenated for 5 days (1 atm, balloon), filtered through a celite pad, rinsed with MeOH and EtOAc and the filtrate was concentrated to afford the title compound **39** (450 mg, 1.27 mmol, 59% yield).

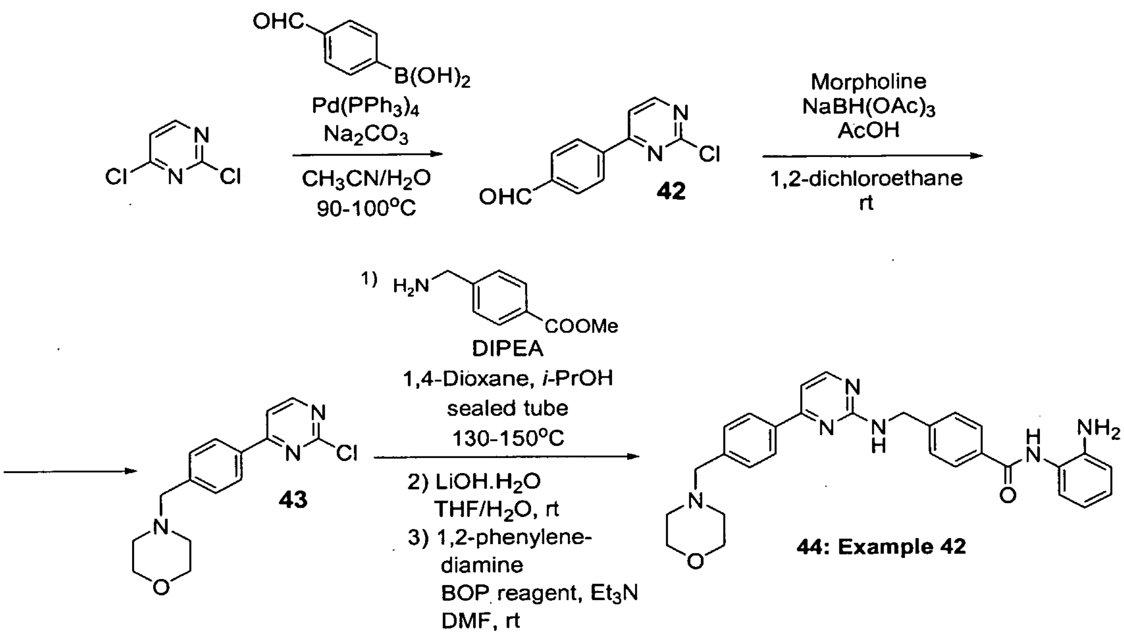
[0365] Step 4: Methyl 4-({4-[4-(2-dimethylamino-ethoxy)-3-fluoro-phenyl]-pyrimidin-2-ylamino}-methyl)-benzoate (40).

[0366] To a solution of **39** (450 mg, 1.27 mmol) in acetone (25 mL) was added 2-(dimethylamino)ethyl chloride hydrochloride (220 mg, 1.53 mmol) followed by potassium iodide (53 mg, 0.32 mmol) and potassium carbonate (878 mg, 6.35 mmol). The reaction mixture was refluxed for 20 h, then saturated solution of NH_4Cl was added, pH of the mixture was adjusted to 8 and acetone was removed under reduced pressure. The formed solid was collected by filtration, washed with water, dried and purified by flash chromatography on silica gel (MeOH/DCM/NH_4OH: 10/89/1) to afford the title compound **40** (525 mg, 1.24 mmol, 97% yield).

[0367] Steps 5: N-(2-Amino-phenyl)-4-({4-[4-(2-dimethylamino-ethoxy)-3-fluoro-phenyl]-pyrimidin-2-ylamino}-methyl)-benzamide (41)

[0368] The title compound **41** (Example 41) was obtained from **40** as off-white solid in two steps following the same procedure as in example 25, steps 5 and 6 (scheme 5). ^1H NMR: (400 MHz, DMSO-d_6) δ (ppm) : 9.55 (s, 1H), 8.27 (d, J = 5.2 Hz, 1H), 7.95-7.75 (m, 5H), 7.50-7.35 (m, 2H), 7.25 (t, J = 8.0 Hz, 1H), 7.14-7.06 (m, 2H), 6.92 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.54 (t, J = 7.6 Hz, 1H), 4.85 (s, 2H), 4.60 (d, J = 5.2 Hz, 2H), 4.17 (t, J = 5.6 Hz, 2H), 2.66 (t, J = 5.6 Hz, 2H), 2.21 (s, 6H).

Scheme 12



Example 42:

N-(2-Amino-phenyl)-4-{[4-(4-morpholin-4-ylmethyl-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide (44)

[0369] Step 1: 4-(2-Chloro-pyrimidin-4-yl)-benzaldehyde (42)

[0370] The title compound **42** was obtained following the same procedure as in example 25, step 1 (scheme 5), starting with 4-formylphenylboronic acid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ (ppm): 10.11 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 8.27 (td, J = 8.4, 1.6 Hz, 2H), 8.03 (td, J = 8.4, 1.6 Hz, 2H), 7.73 (d, J = 4.8 Hz, 1H).

[0371] Step 2: 4-[4-(2-Chloro-pyrimidin-4-yl)-benzyl]-morpholine (43)

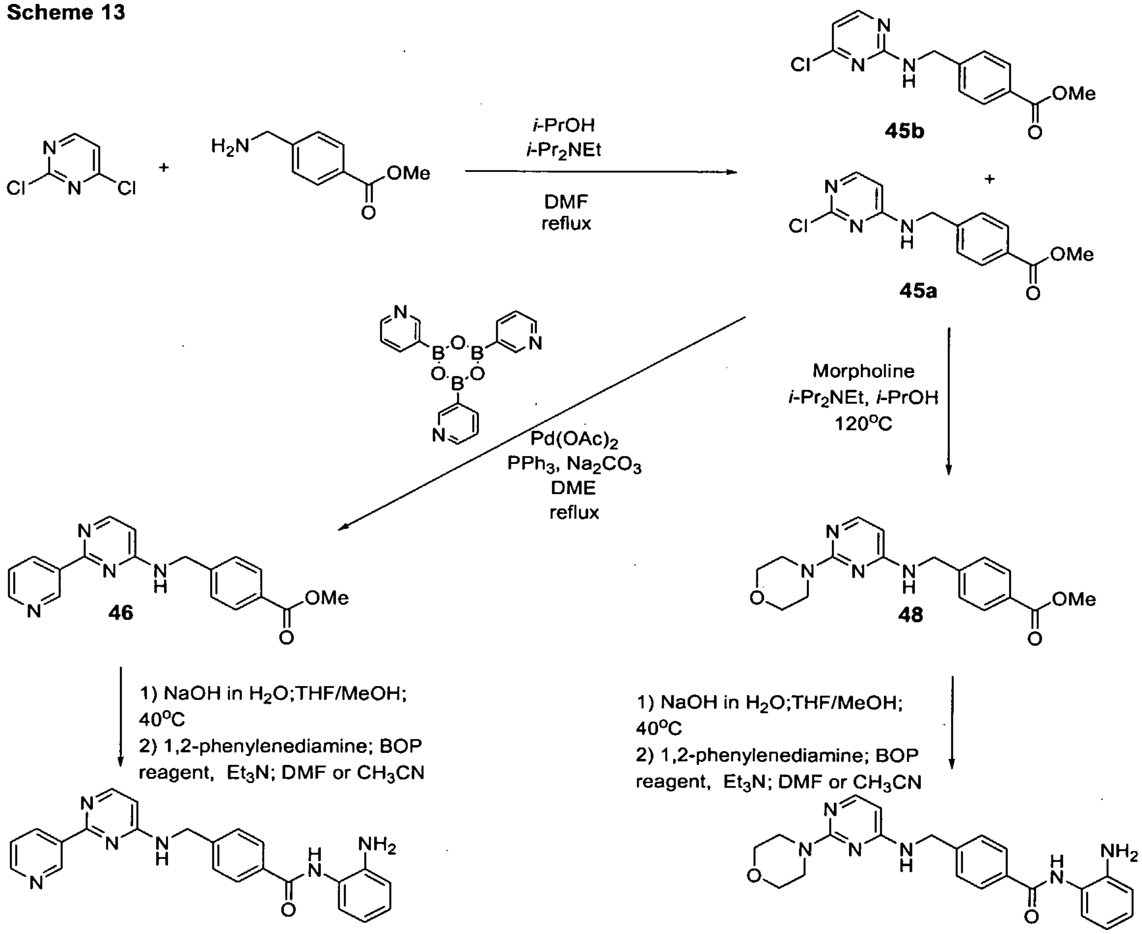
[0372] To a solution of **42** (950 mg, 4.35 mmol) and morpholine (455 μL, 5.21 mmol) in dry 1,2-dichloroethane (10 mL) at room temperature was added AcOH (2 drops) followed by $NaBH(OAc)_3$ (1.1 g, 5.21 mmol) and the mixture was stirred for 16 h. A solution of 10% K_2CO_3 was added to the reaction mixture followed by dichloromethane and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and organic layer was dried over anhydrous Na_2SO_4, filtered to form a residue which was purified by flash chromatography on silica gel ($EtOAc/CH_2Cl_2$: 20/80) to afford the title compound **43** (460 mg, 1.59 mmol, 36% yield).

[0373] Steps 3: N-(2-Amino-phenyl)-4-{[4-(4-morpholin-4-ylmethyl-phenyl)-pyrimidin-2-ylamino]-methyl}-benzamide (44)

[0374] The title compound **44** was obtained from **43** in three steps following the same procedure as in example 2, steps 2-4 (scheme 2) and was isolated as the hydrochloride salt by

dissolving it in a mixture of dichloromethane and EtOAc by adding a 1N HCl in Et_2O solution. The precipitate was filtered off, washed with EtOAc and dried under high vacuum. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.33 (d, J = 5.2 Hz, 1H), 8.00-7.93 (m, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.4 Hz, 1H), 7.07 (td, J = 7.6, 1.2 Hz, 1H), 7.00 (d, J = 5.2 Hz, 1H), 6.85-6.78 (m, 2H), 5.83 (t, J = 6.0 Hz, 1H), 4.78 (d, J = 6.0 Hz, 2H), 3.74 (t, J = 4.0 Hz, 4H), 3.59 (s, 2H), 2.51 (bs, 4H).

Scheme 13



47: Example 43 **49: Example 44**

Example 43:

N-(2-Amino-phenyl)-4-[(2-pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzamide (47)

[0375] Step 1: 4-[(2-Chloro-pyrimidin-4-ylamino)-methyl]-benzoic acid methyl ester (45a) and 4-[(4-chloro-pyrimidin-2-ylamino)-methyl]-benzoic acid methyl ester (45b)

[0376] A mixture of 2,4-dichloropyrimidine (4.51 g, 30.3 mmol), methyl 4-aminomethyl-benzoate (5.00 g, 30.3 mmol), DIPEA (10.4 mL, 60.6 mmol) in *i*-PrOH (60 mL) and DMF (40 mL) was refluxed for 5 h. After evaporation of the reaction mixture to dryness the residue was purified by flash chromatography on silica gel (EtOAc/hexane: 40/60→60/40 + 1% of Et_3N) to afford the

title compounds **45a** (3.454 g, 41% yield) and **45b** (1.52 g, 14% yield, contaminated with the starting material).

45a, ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 8.45 (bs, 1H), 7.90-7.94 (m, 3H), 7.42 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 5.9 Hz, 1H), 4.58 (d, J = 5.3 Hz, 2H), 3.83 (s, 3H)).

45b, ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 8.27 (t, J = 6.5 Hz, 1H), 8.21 (bs, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 6.69 (d, J = 5.1 Hz, 1H), 4.55 (bs, 2H), 3.82 (s, 3H).

[0377] Step 2: Methyl 4-[(2-Pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzoate (46)

[0378] To a suspension of 3-pyridine boroxin (189 mg, 0.60 mmol), **45a** (500 mg, 1.81 mmol), $Pd(OAc)_2$ (41 mg, 0.18 mmol) and PPh_3 (95 mg, 0.36 mmol) in DME (1.8 mL) was added a solution of Na_2CO_3 (590 mg dissolved in the minimum quantity of water, 5.60 mmol) at room temperature. The reaction mixture was purged with nitrogen and refluxed for 4 days, evaporated to dryness and purified by flash chromatography on silica gel (EtOAc/hexane: 30/70 + 1% of Et_3N) to afford the title compound **46** (152 mg, 26% yield) as a pale yellow solid.

[0379] Step 3,: N-(2-Amino-phenyl)-4-[(2-pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzamide (47)

[0380] The title compound **47** (example 43) was obtained from **46** as an off-white solid in two steps following the same procedure as in Example **34**, step 3 (reactions 3 and 4) (Scheme 7). ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.50 (s, 1H), 9.30 (d, J = 1.6 Hz, 1H), 8.54 (dd, J= 4.7, 1.6 Hz, 1H), 8.46 (ddd, J = 8.0, 2.0, 2.0 Hz, 1H), 8.11 (dd, J 6.3, 6.1 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H), 7.38-7.43 (m, 3H), 7.05 (m, 1H), 6.86 (m, 1H), 6.67 (dd, J = 7.9, 1.5 Hz, 1H), 6.49 (m, 2H), 4.79 (s, 2H), 4.66 (s, 2 H).

Example 44:

***N*-(2-Amino-phenyl)-4-[(2-morpholin-4-yl-pyrimidin-4-ylamino)-methyl]-benzamide (49)**

[0381] Step 2: Methyl 4-[(2-morpholin-4-yl-pyrimidin-4-ylamino)-methyl]-benzoate (48a)

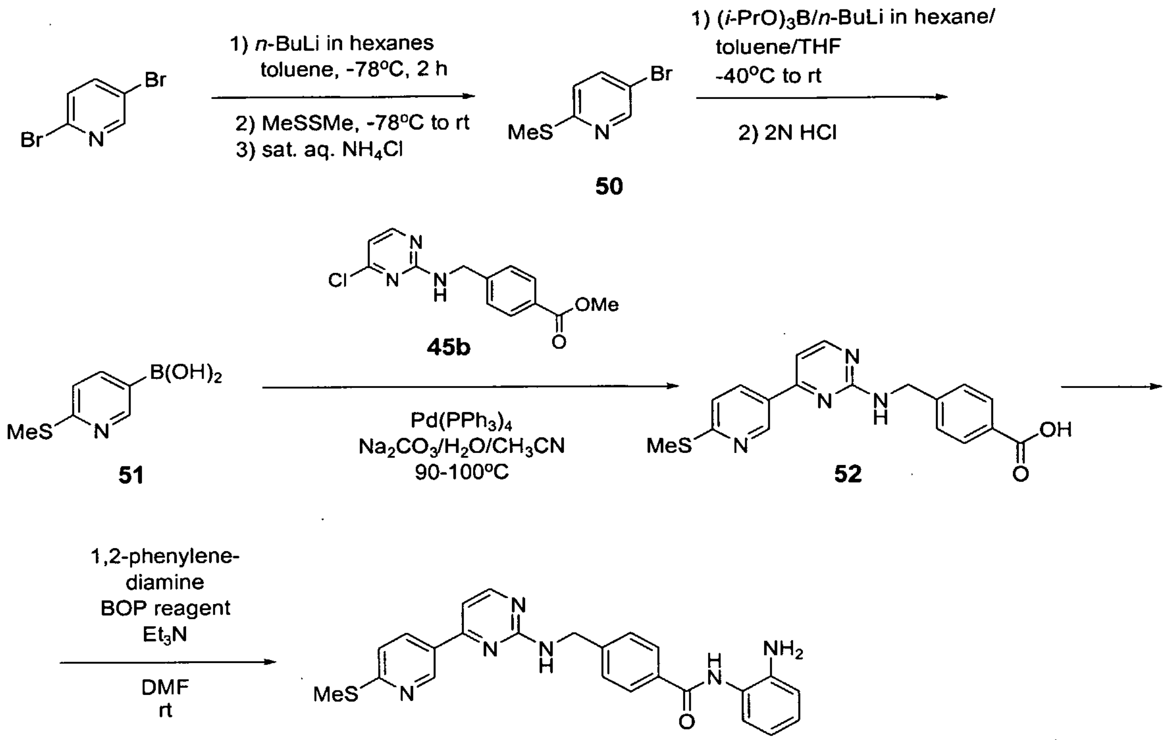
[0382] A mixture of **45a** (2.50 g, 9.0 mmol), morpholine (0.95 mL, 10.8 mmol) and *i*-Pr_2NEt (3.12 mmol) in *i*-PrOH (18.0 mL) in a sealed flask was heated at 120□C overnight and cooled down to room temperature. A precipitate was formed which was collected by filtration, rinsed with *i*-PrOH and dried to afford the title compound **48** (2.96 g, quantitative yield).

[0383] Step 3: N-(2-Amino-phenyl)-4-[(2-morpholin-4-yl-pyrimidin-4-ylamino)-methyl]-benzamide (49)

[0384] The title compound **49** (example 44) was obtained from **48** as an off-white solid in two steps following the same procedure as in example 34, step 3 (reactions 3 and 4) (scheme 7). ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.56 (s, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 5.7 Hz,

1H), 7.56 (bs, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.8 Hz, 1H), 6.94 (m, 1H), 6.75 (m, 1H), 6.57 (m, 1H), 5.83 (bs, 1H), 4.87 (s, 2H), 4.51 (bs, 2H), 3.56 (s, 8H).

Scheme 14



53: Example 45

Example 45:

N-(2-Amino-phenyl)-4-{[4-(6-methylsulfanyl-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (53)

[0385] Step 1: 5-Bromo-2-methylsulfanyl-pyridine (50)

[0386] To a stirred solution of 2,5-dibromopyridine (5.00 g, 21.11 mmol) in anhydrous toluene (300 mL) at −78□C under nitrogen was slowly added a solution of *n*-BuLi (10.13 mL, 25.33 mmol, 2.5M in hexanes). After 2 h at −78□C, methyl disulfide (2.47 mL, 27.44 mmol) was added. The reaction mixture was stirred for 1 h at −78□C and was allowed to warm to room temperature, quenched with saturated NH_4Cl to form a two-phase system. The organic layer was separated, washed with sat NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (AcOEt/hexane, 5/95) to afford the title compound **50** (2.74 g, 13.43 mmol, 64% yield) as a pale yellow oily liquid. ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.49 (dd, J = 2.3, 0.6 Hz, 1H), 7.60 (dd, J = 8.5, 2.4 Hz, 1H), 7.09 (dd, J = 8.6, 0.8 Hz, 1H), 2.57 (s, 3H).

[0387] Step 2: 5-(2-methylsulfanyl-pyridinyl)-boronic acid (51)

[0388] To a stirred solution of **50** (2.74 g, 13.43 mmol) and triisopropylborate (3.72 mL, 16.11 mmol) in a mixture of anhydrous toluene/THF (20 mL/5 mL) at −40□C under nitrogen was added dropwise a solution of *n*-BuLi (6.98 mL, 17.45 mmol, 2.5M in hexanes). After stirring for 1 h at −40□C, the mixture was allowed to warm to room temperature and quenched with 2N HCl. The resultant suspension was filtered; the precipitate was rinsed with H_2O and AcOEt. The filtrate was neutralized with 1N NaOH (pH 7) and extracted with AcOEt. The organic layer and the precipitate were combined, solvent was evaporated and the solid residue was triturated with MeCN-MeOH to afford the title compound **51** (1.84 g, 10.88 mmol, 81% yield) as a pale yellow solid.

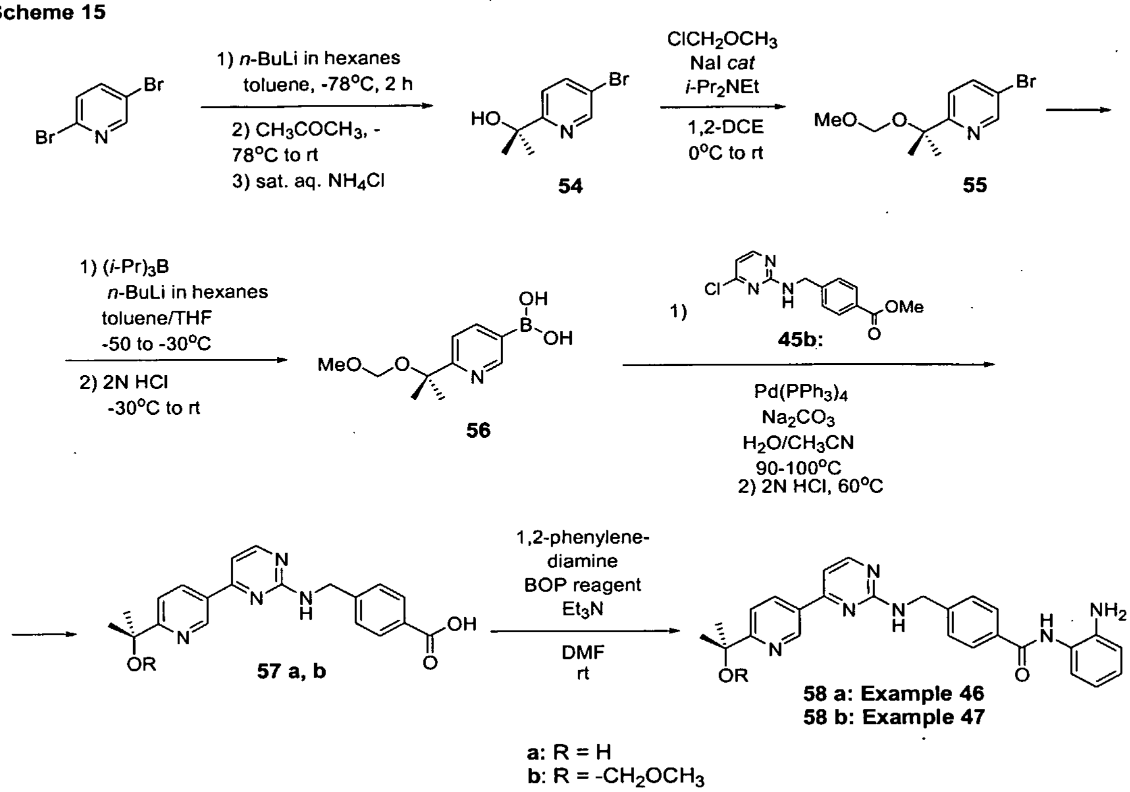
[0389] Step 3: 4-{[4-(6-Methylsulfanyl-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzoic acid (52)

[0390] To a degassed stirred suspension of a mixture of **51** (593 mg, 3.51 mmol), **45b** (500 mg, 1.80 mmol) and solution of Na_2CO_3 (15 mL, 0.4M) in acetonitrile (15 mL) at room temperature $Pd(PPh_3)_4$ (126 mg, 0.11 mmol) was added. The reaction mixture was heated at 90-95□C for 24 h under nitrogen. Then, 1M NaOH (amount) was added and the heating was continued for additional 2 h. After cooling to the room temperature the reaction mixture was filtered, filtrate was extracted with AcOEt, the aqueous layer was collected, filtered, concentrated and acidified with 2N HCl (pH at 5-6). A precipitate was formed which was collected by filtration and dried to afford the title compound **52** (396 mg, 1.12 mmol, 62% yield) as a beige solid.

[0391] Step 4: N-(2-Amino-phenyl)-4-{[4-(6-methylsulfanyl-pyridin-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (53)

[0392] The title compound **53** (example 45) was obtained from **52** as an off-white solid in one step following the same procedure as in example 2, step 4 (scheme 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.60 (s, 1H), 9.12 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 5.3 Hz 1H), 8.29 (bd, J = 8.0 Hz, 1H), 7.98 (t, J = 6.4 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.56-7.38 (m, 3H), 7.24 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 7.0 Hz, 1H), 6.98 (td, J = 7.5, 1.4 Hz, 1H), 6.79 (dd, J = 7.9, 1.3 Hz 1H), 6.60 (td, J = 7.2, 1.2 Hz, 1H), 4.90 (s, 2H), 4.67 (bd, J = 6.3 Hz, 2H), 2.60 (s, 3H).

Scheme 15



Example 46:

N-(2-Amino-phenyl)-4-({4-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-pyrimidin-2-ylamino}-methyl)-benzamide (58a)

[0393] Step 1: 2-(5-Bromo-pyridin-2-yl)-propan-2-ol (54a)

[0394] To a stirred solution of 2,5-dibromopyridine (2.00 g, 8.44 mmol) in anhydrous toluene (100 mL) at −78□C under nitrogen was slowly added a solution of *n*-BuLi (4.05 mL, 10.13 mmol, 2.5M in hexanes). After 2 h at −78□C, acetone (806 µl, 10.98 mmol) was added. After stirring for 1 h, the reaction mixture was allowed to warm to 0□C and was quenched with a saturated NH_4Cl. A two-phase system was formed; the organic layer was separated, washed with saturated NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 20/80) to afford the title compound **54** (1.37 g, 6.34 mmol, 75% yield) as a pale yellow oily liquid. ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): ABX System (δ_A = 7.32, δ_B = 7.82, δ_X = 8.58, J_{AB} = 8.4 Hz, J_{BX} = 2.3 Hz, J_{AX} = 0 Hz, 3H), 4.47 (bs,1H), 1.57 (s, 6H).

[0395] Step 2: 5-Bromo-2-(1-methoxymethoxy-1-methyl-ethyl)-pyridine: (55)

[0396] To a stirred solution of **54** (1.36 g, 6.29 mmol) and *i*-Pr_2NEt (2.19 mL, 12.59 mmol) in anhydrous dichloromethane (20 mL) at 0□C under nitrogen was slowly added chloromethyl

methyl ether (1.17 mL, 14.63 mmol). After 30 min, the reaction mixture was allowed to warm to room temperature, stirred for two days, concentrated and purified by flash chromatography on silica gel (AcOEt/hexane: 5/95) to afford the title compound **55** (1.56 g, 6.00 mmol, 95% yield) as a pale yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): ABX System (δ_A = 7.50, δ_B = 7.80, δ_X = 8.60, J_{AB} = 8.4 Hz, J_{BX} = 2.4 Hz, J_{AX} = 0.8 Hz, 3H), 4.73 (s,2H), 3.41 (s, 3H), 1.64 (s, 6H)).

[0397] Step 3: 5-(2-[1-methoxymethoxy-1-methyl-ethyl]-pyridinyl)-boronic acid (56)

[0398] To a stirred solution of **55** (2.90 g, 11.15 mmol) and triisopropylborate (3.09 mL, 13.38 mmol) in a mixture of anhydrous toluene/THF (20 mL/5 mL) at −50°C under nitrogen was added dropwise a solution of *n*-BuLi (7.87 mL, 13.38 mmol, 1.7M in hexanes) over 10 min. After 45 min at −50°C, the mixture was allowed to warm to room temperature and was quenched with 2N HCl (30 mL) at −30°C. After decantation, the pH of the aqueous layer was adjusted to 7 with 1N NaOH, and extracted with AcOEt. The extract was evaporated and the residue was dried under vacuum to afford the title compound **56a** (2.33 g, 10.37 mmol, 93% yield) as beige sticky foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): ABX System (δ_A = 7.55, δ_B = 8.11, δ_X = 8.83, J_{AB} = 7.8 Hz, J_{BX} = 1.8 Hz, J_{AX} = 0.9 Hz, 3H), 8.32 (s, 2H), 4.68 (s, 2H), 3.31 (s, 3H), 1.56 (s, 6H)).

[0399] Step 4: 4-({4-[6-(1-Hydroxy-1-methyl-ethyl)-pyridin-3-yl]-pyrimidin-2-ylamino}-methyl)-benzoic acid (57a)

[0400] To a degassed stirred suspension of a mixture of **56** (550 mg, 2.44 mmol), **45b** (510 mg, 1.84 mmol, not pure) and an aqueous solution of Na_2CO_3 (10 mL, 0.4M) in acetonitrile (15 mL) at room temperature $Pd(PPh_3)_4$ (106 mg, 0.09 mmol) was added. The reaction mixture was heated at 95-100°C for 24 h under nitrogen, cooled to room temperature, filtered, filtrate was concentrated, diluted with water, washed with AcOEt, acidified with 2N HCl (25 mL) and warmed at 60°C for 4 h. The reaction mixture was allowed to cool to room temperature and the pH was adjusted to 5-6 with 2N NaOH. A precipitate formed which was collected by filtration, rinsed with water and dried to afford the title compound **57a** (303 mg, 0.83 mmol, 45% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.82 (bs, 1H), 9.20-9.08 (m, 1H), 8.46-8.32 (m, 2H, included at 8.40 ppm, d, J = 5.1 Hz), 7.98 (t, J = 6.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.84-7.72 (m, 1H), 7.58-7.42 (m, 2H), 7.25 (d, J = 5.1 Hz, 1H), 5.34 (s,1H), 4.67 (d, J = 5.7 Hz, 2H), 1.50 (s, 6H).

[0401] Step 5: N-(2-Amino-phenyl)-4-({4-[6-(1-hydroxy-1-methyl-ethyl)-pyridin-3-yl]-pyrimidin-2-ylamino}-methyl)-benzamide (58a)

[0402] The title compound **58a** (example 46) was obtained from **57a** as off-white solid in one step following the same procedure as in Example 2, step 4 (Scheme 2). ^{1}H NMR (400 MHz,

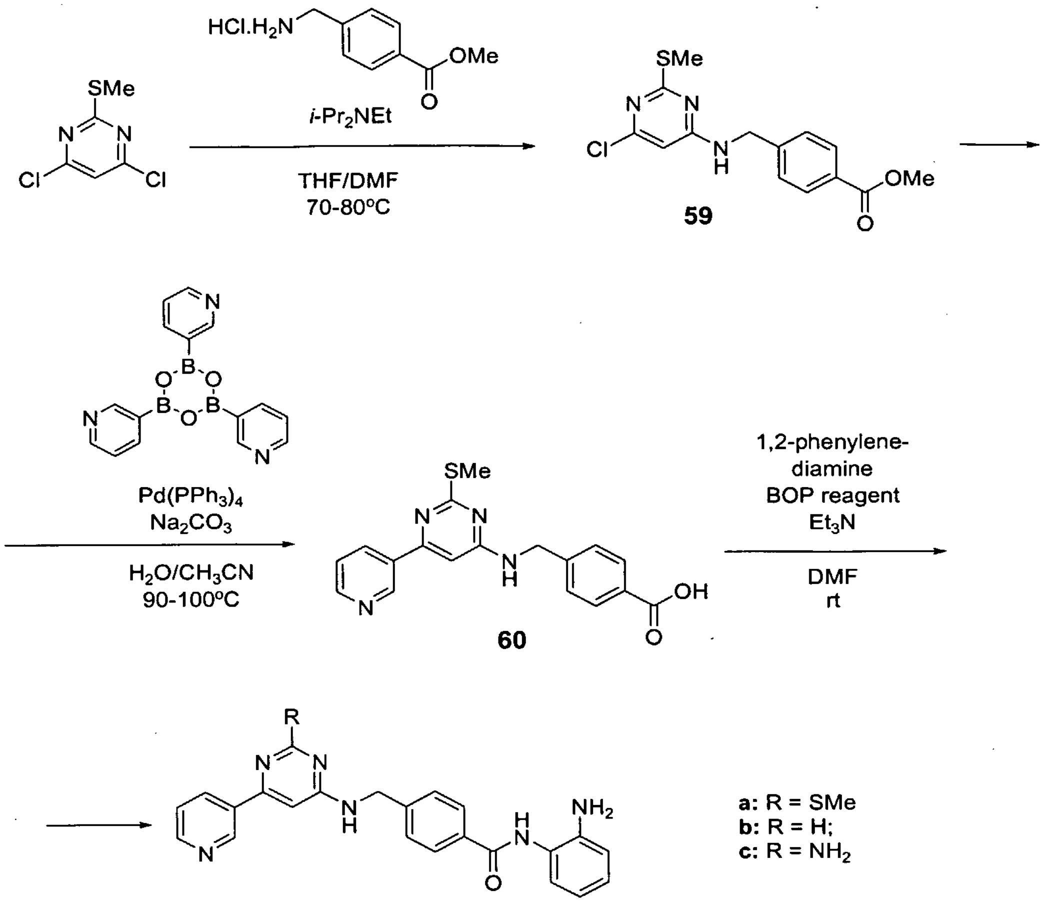
DMSO-d_6) δ(ppm): 9.60 (s, 1H), 9.15 (d, J = 2.0 Hz, 1H), 8.45-8.35 (m, 2H, included at 8.41 ppm, d, J = 5.1 Hz), 8.00 (t, J = 6.4 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.79 (bd, J = 8.2 Hz, 1H), 7.58-7.43 (m, 2H), 7.25 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 6.98 (td, J = 7.6, 1.5 Hz, 1H), 6.78 (dd, J = 8.0, 1.4 Hz 1H), 6.60 (t, J = 7.4 Hz, 1H), 5.37 (s,1H), 4.90 (s, 2H), 4.68 (d, J = 5.7 Hz, 2H), 1.50 (s, 6H).

Example 47:

***N*-(2-Amino-phenyl)-4-({4-[6-(1-methoxymethoxy-1-methyl-ethyl)-pyridin-3-yl]-pyrimidin-2-ylamino}-methyl)-benzamide (58b)**

[0403] The title compound **58b** (example 47) was obtained from **56a** as off-white solid in two steps following the same procedures as in example 46, step 4 (note: no acid hydrolysis at 60□C) and 5 (Scheme 15). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.61 (s, 1H), 9.18 (s, 1H), 8.50-8.32 (m, 2H, included at 8.42 ppm, d, J = 5.1 Hz), 8.02 (t, J = 6.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.72 (bd, J = 7.6 Hz, 1H), 7.59-7.42 (m, 2H), 7.26 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.98 (td, J = 7.6, 1.4 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.60 (t, J = 7.4 Hz, 1H), 4.91 (s, 2H), 4.72 (s, 2H), 4.68 (d, J = 5.3 Hz, 2H), 3.32 (s, 3H), 1.60 (s, 6H).

Scheme 16



61a: Example 48
61b: Example 49
61c: Example 50

Example 48:

N-(2-Amino-phenyl)-4-[(2-methylsulfanyl-6-pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzamide (61a)

[0404] Step 1: Methyl 4-[(6-Chloro-2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-benzoate (59)

[0405] A stirred suspension of 4,6-dichloro-2-(methylthio)pyrimidine (657 mg, 3.37 mmol) or 4,6-dichloro-2-(R)-pyrimidine, methyl 4-(aminomethyl)benzoate.HCl (744 mg, 3.69 mmol) and *i*-Pr_2NEt (2.34 mL, 13.43 mmol) in a mixture of anhydrous THF/DMF (10 mL/2 mL) under nitrogen was heated at 70-80□C for 24 h. The mixture was allowed to cool down to room temperature, poured into a saturated $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with water, saturated NH_4Cl, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (eluent AcOEt/CH_2Cl_2, 30/70, then 40/60) to afford the title compound **59a** (929 mg, 2.87 mmol, 85% yield) as a beige powder.

[0406] Step 2: 4-[(2-Methylsulfanyl-6-pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzoic acid (60)

[0407] To a degassed stirred suspension of a mixture of **59** (925 mg, 2.86 mmol), 2,4,6-(3-pyridinyl)-cyclotriboroxane (360 mg, 1.14 mmol) and aqueous of Na_2CO_3 (20 mL, 0.4M) in acetonitrile (20 mL) at room temperature was $Pd(PPh_3)_4$ (165 mg, 0.14 mmol) was added. The reaction mixture was heated at 95for one to two days under nitrogen. 1M NaOH (5 mL) was added to the reaction mixture and the heating was maintained for another 1 h. The mixture was allowed to cool to room temperature and filtered. The filtrate was extracted with AcOEt, the aqueous layer was separated, concentrated, and acidified with 2N HCl (pH at 5-7). A precipitate formed which was collected by filtration and dried to afford the title compound **60** (770 mg, 2.19 mmol, 76% yield) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.89 (bs 1H), 9.15 (bs, 1H), 8.72-8.64 (m, 1H), 8.39-8.20 (m, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.58-7.40 (m, 3H), 6.84 (s, 1H), 4.69 (d, J = 5.1 Hz 2H), 2.48 (bs, 3H).

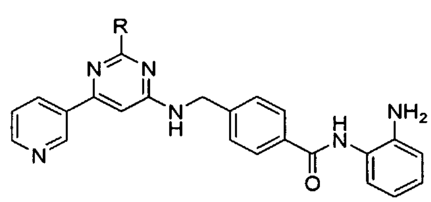
[0408] Step 3: N-(2-Amino-phenyl)-4-[(2-methylsulfanyl-6-pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzamide (61a)

[0409] The title compound **61a** (Example 48) was obtained from **60** as off-white solid in one step following the same procedure as in example 2, step 4 (scheme 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.64 (s, 1H), 9.16 (bs, 1H), 8.68 (dd, J = 4.7, 1.6 Hz 1H), 8.45-8.25 (m, 1H), 8.27 (t, J = 5.9 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.58-7.42 (m, 3H), 7.17 (d, J = 7.6 Hz, 1H), 6.98 (td, J = 7.5, 1.4 Hz, 1H), 6.85 (s, 1H), 6.79 (dd, J = 7.9, 1.1 Hz 1H), 6.61 (t, J = 7.2 Hz, 1H), 4.92 (s, 2H), 4.69 (bs, 2H), 2.50 (s, 3H).

Examples 49-50:

[0410] **Examples 49, 50** (compounds **61b-c**) were prepared using the same procedures as described for compound **61a** (example 48, scheme 16).

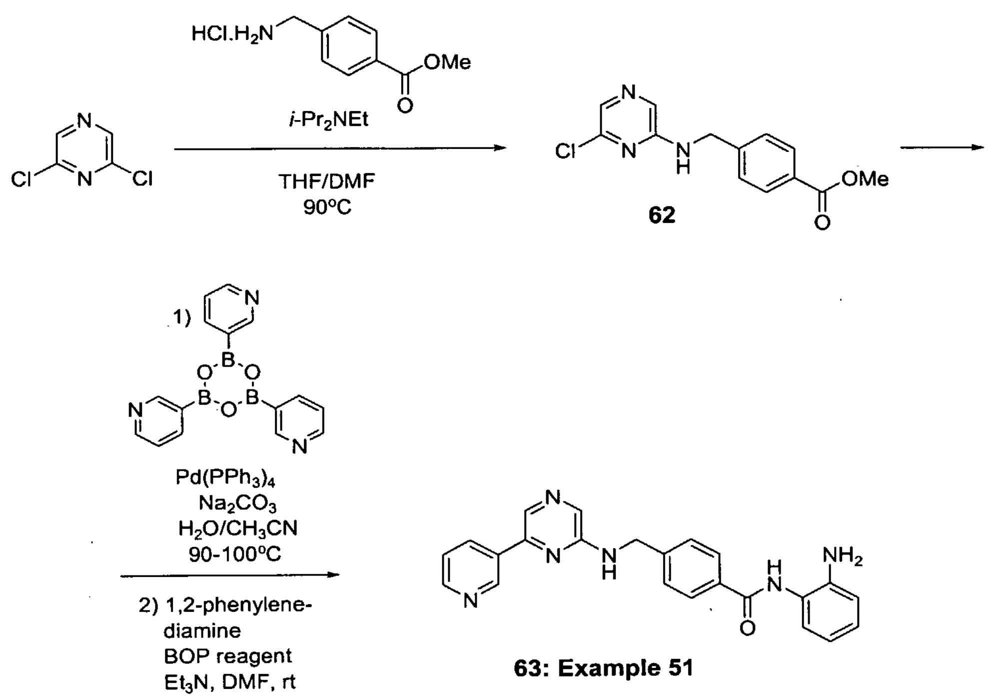
Table 5



Cmpd	Ex	R	Name	Characterization
61b	**49**	**H**	*N*-(2-Amino-phenyl)-4-[(6-pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.64 (s, 1H), 9.19 (bs, 1H), 8.69 (d, J = 3.7 Hz 1H), 8.56 (s, 1H), 8.36 (d, J = 6.3 Hz, 1H), 8.20 (t, J = 6.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.52-7.40 (m, 3H), 7.17 (d, J = 7.0 Hz, 1H), 7.13 (s, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 7.6 Hz 1H), 6.61 (t, J = 7.5 Hz, 1H), 4.92 (s, 2H), 4.71 (bs, 2H).

Cmpd	Ex	R	Name	Characterization
61c	**50**	**NH_2**	*N*-(2-Amino-phenyl)-4-[(2-amino-6-pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.63 (s, 1H), 9.08 (d, J = 1.8 Hz, 1H), 8.63 (dd, J = 4.7, 1.6 Hz 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.63 (bs, 1H), 7.54-7.43 (m, 3H), 7.17 (d, J = 7.2 Hz, 1H), 6.98 (td, J = 7.6, 1.2 Hz, 1H), 6.79 (d, J = 6.8 Hz 1H), 6.61 (t, J = 7.5 Hz, 1H), 6.38 (s, 1H), 6.19 (bs, 2H).4.92 (s, 2H), 4.65 (bs, 2H).

Scheme 17



63: Example 51

Example 51:

N-(2-Amino-phenyl)-4-[(6-pyridin-3-yl-pyrazin-2-ylamino)-methyl]-benzamide (63)

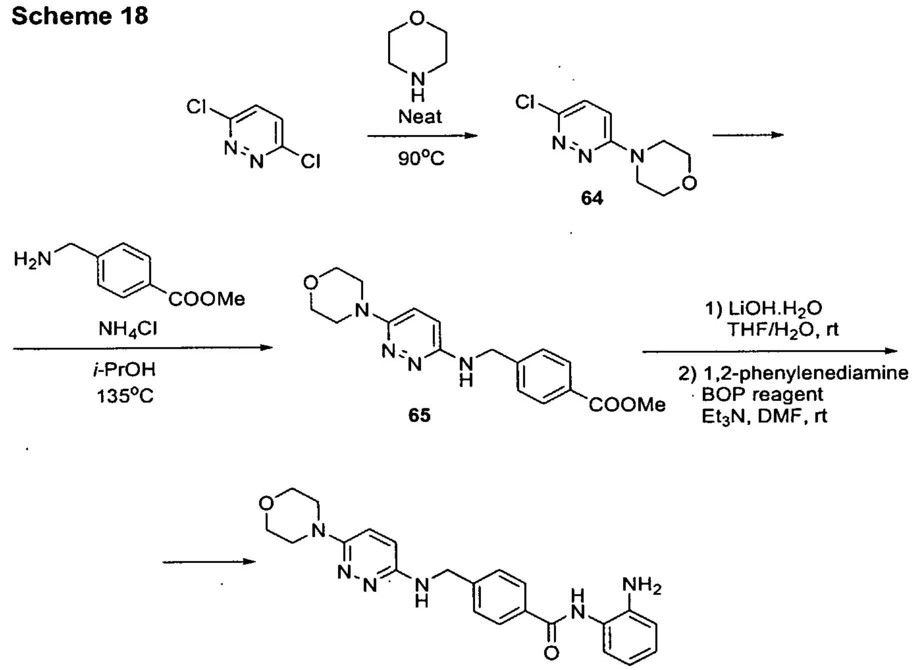
[0411] Step 1: 4-[(6-Chloro-pyrazin-2-ylamino)-methyl]-benzoic acid methyl ester (62)

[0412] A stirred suspension of 2,6-dichloropyrazine (500 mg, 3.36 mmol), methyl 4-(aminomethyl)benzoate.HCl (744 mg, 3.69 mmol) and *i*-Pr_2NEt (2.05 mL, 11.75 mmol) in a mixture of anhydrous THF/DMF (10 mL/2 mL) under nitrogen was heated at 90□C for 24 h. The mixture was allowed to cool down to room temperature, was poured into saturated aqueous NH_4Cl and extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (AcOEt/CH_2Cl_2: 20/80→30/70) to afford the title compound **62** (300 mg, 1.08 mmol, 32% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 8.18 (t, J = 6.0 Hz, 1H), 7.97 (s, 1H), AB system (δ_A = 7.95, δ_B = 7.49, J_{AB} = 8.5 Hz, 4H), 7.75 (s, 1H), 4.58 (d, J = 5.9 Hz, 2H), 3.87 (s, 3H).

[0413] Step 2: N-(2-Amino-phenyl)-4-[(6-pyridin-3-yl-pyrazin-2-ylamino)-methyl]-benzamide (63)

[0414] The title compound **63** (example 51) was obtained from **62** as a beige powder in two steps following the same procedure as in Example 48, steps 2 and 3 (Scheme 16). ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) : 9.62 (s, 1H), 9.19 (dd, J = 2.3, 0.8 Hz, 1H), 8.62 (dd, J = 4.7, 1.6 Hz 1H), 8.40 (s, 1H), 8.36 (ddd, J = 8.4, 2.0, 2.0 Hz, 1H), 8.06 (s, 1H), 8.01-7.92 (m,3H), 7.54 (d, J = 8.2 Hz, 2H), 7.51 (ddd, J = 7.8, 4.7, 0.8 Hz, 1H), 7.16 (bd, J = 6.7 Hz, 1H), 6.98 (td, J = 7.6, 1.5 Hz, 1H), 6.78 (dd, J = 8.0, 1.4 Hz 1H), 6.60 (td, J = 7.5, 1.3 Hz, 1H), 4.91 (s, 2H), 4.71 (d, J = 6.1 Hz, 2H).

Scheme 18



66: Example 52

<u>**Example 52:**</u>

***N*-(2-Amino-phenyl)-4-[(6-morpholin-4-yl-pyridazin-3-ylamino)-methyl]-benzamide (66)**

[0415] <u>Step 1: 4-(6-Chloro-pyridazin-3-yl)-morpholine (64)</u>

[0416] A 50 mL flask equipped with a reflux condenser was charged with morpholine (2.93 mL, 33.5 mmol) and 3,6-dichloropyridazine (5.00 g, 33.5 mmol). The mixture was heated at 90°C for 6 h, the resultant solid was partitioned between EtOAc, water and saturated NH_4Cl. Organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated to afford the title compound **64** (5.3 g, 26.5 mmol, 79% yield).

[0417] <u>Step 2: Methyl 4-[(6-morpholin-4-yl-pyridazin-3-ylamino)-methyl]-benzoate (65)</u>

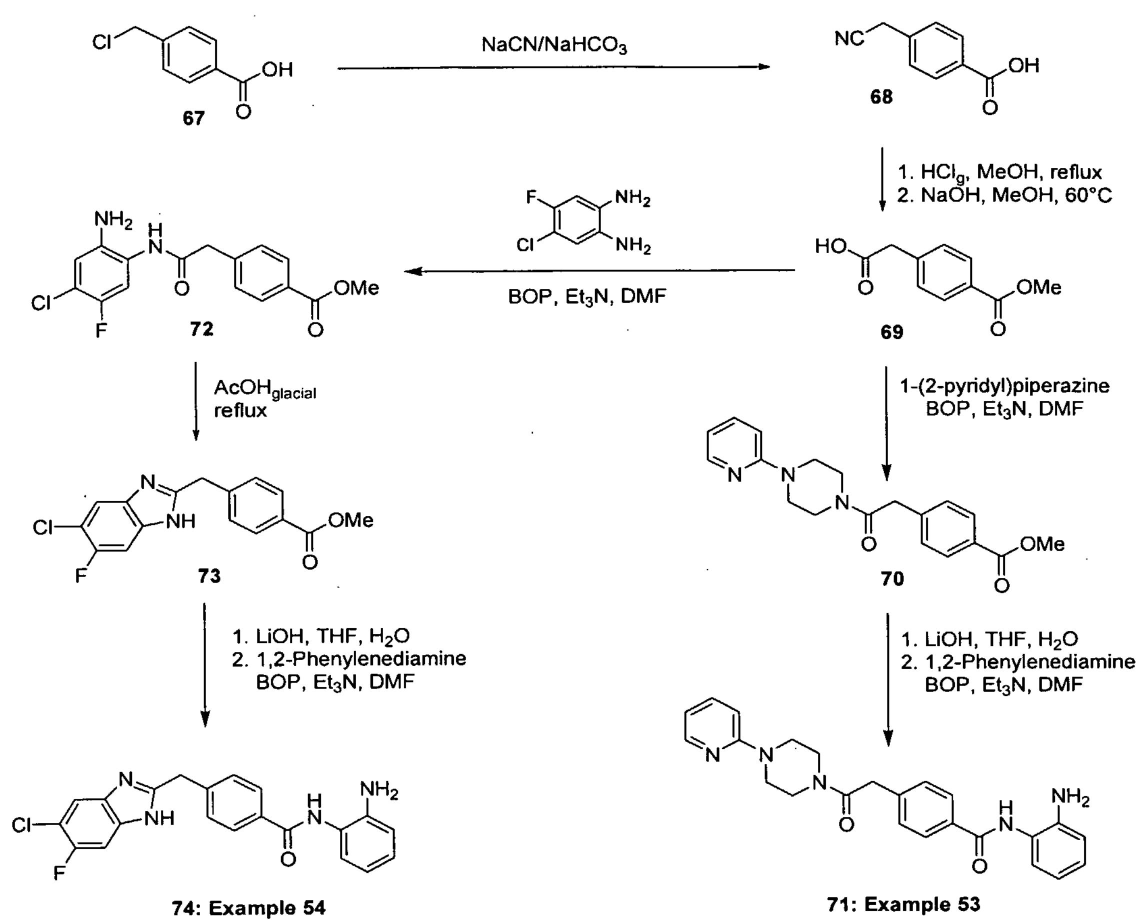
[0418] To a solution of **64** (2.0 g, 10.0 mmol) and methyl 4-(aminomethyl)benzoate hydrochloride (2.2 g, 11.0 mmol) in *i*-PrOH (200 mL) was added NH_4Cl (2.14 g, 40.0 mmol). The reaction mixture was heated at 150°C for 72 h and concentrated. The residue was dissolved in

water and the aqueous phase was extracted with. \the aqueous phase was separated, treated with 1N NaOH (pH 8) and extracted with EtOAc. The extract was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 2/98 to 5/95) to afford the title compound **65** (270 mg, 0.82 mmol, 8% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ (ppm) : 7.97 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 9.2 Hz, 1H), 6.69 (d, J = 9.2 Hz, 1H), 5.16-5.06 (bs, 1H), 4.67 (s, 2H), 3.90 (s, 3H), 3.82 (t, J = 4.8 Hz, 4H), 3.41 (t, J = 4.8 Hz, 4H).

[0419] <u>Steps 3: N-(2-Amino-phenyl)-4-[(6-morpholin-4-yl-pyridazin-3-ylamino)-methyl]-benzamide (66)</u>

[0420] The title compound **66** (example 52) was obtained from **65** as an off-white solid in two steps following the same procedure as in Example 2, steps 3 and 4 (Scheme 2). ^1H NMR: (400 MHz, DMSO-d_6) δ (ppm): 9.57 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.15-7.12 (m, 1H), 7.13 (d, J = 9.6 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.88 (t, J = 6.0 Hz, 1H), 6.83 (d, J = 9.6 Hz, 1H), 6.75 (dd, J = 8.0, 1.2 Hz, 1H), 6.57 (t, J = 8.0 Hz, 1H), 4.86 (s, 2H), 4.54 (d, J = 6.4 Hz, 2H), 3.69 (t, J = 4.8 Hz, 4H), 3.24 (t, J = 4.8 Hz, 4H).

Scheme 19



Example 53

N-(2-Amino-phenyl)-4-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-benzamide (71)

[0421] Step 1: 4-Cyanomethyl-benzoic acid (68).

[0422] The title compound was obtained according to the procedure described in *J. Med. Chem.* **1997**, 40, 377-384, starting from 4-chloromethylbenzoic acid (**67**).

[0423] Step 2: 4-Carboxymethyl-benzoic acid methyl ester (69).

[0424] The title compound was obtained according to the procedures described in *J. Med. Chem.* 1998, 41, 5219-5246, as a beige solid (85% yield). ^{1}H NMR (DMSO-d_6) δ (ppm): 12.49 (s, 1H), 7.89 (d, J = 1.8 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 2H).

[0425] Step 3: Methyl 4-[2-Oxo-2-(4-pyridin-2-yl-piperazin-1-yl)-ethyl]-benzoate (70).

[0426] Following the procedure described in example 1, step 5 (scheme 1) the title compound **70** was obtained as a pale yellow solid (70% yield). ^{1}H-NMR (DMSO) δ: 8.36 (d, J = 4.7 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.65 (t, J = 4.8 Hz, 1H), 3.87 (s, 2H), 3.83 (s, 3H), 3.71-3.66 (m, 4H), 3.60-3.53 (m, 4H).

[0427] Step 4: N-(2-Amino-phenyl)-4-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-benzamide (71).

[0428] Following the procedures described in Example 1 steps 4 and 5 the title compound **71** was obtained as a beige solid (225 mg, 69%). ^{1}H NMR: (DMSO) δ (ppm): 9.62 (s, 1H), 8.36 (d, J = 4.7 Hz, 2H), 7:90 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 6.8 Hz, 1H), 6.95 (td, J = 7.5, 1.4 Hz, 1H), 6.76 (dd, J = 8.0, 1.4 Hz, 1H), 6.70 (t, J = 4.8 Hz, 1H), 6.57 (tdd, J = 7.6, 1.4 Hz, 1H), 4.90 (s, 2H), 3.87 (s, 2H), 3.72-3.68 (m, 4H), 3.62-3.55 (m, 4H).

Example 54

N-(2-Amino-phenyl)-4-(5-chloro-6-fluoro-1H-benzoimidazol-2-ylmethyl)-benzamide (74).

[0429] Step 1: 4-[(2-Amino-4-chloro-5-fluoro-phenylcarbamoyl)-methyl]-benzoic acid methyl ester (72).

[0430] Following the procedure described in example 1, step 5 (scheme 1) the title compound **72** was obtained as orange oil (69% yield). LRMS: 336.1 (calc.), 337.5 (obt.).

[0431] Step 2: 4-(5-Chloro-6-fluoro-1H-benzoimidazol-2-ylmethyl)-benzoic acid methyl ester (73).

[0432] Compound **72** (333 mg, 0.99 mmol) was dissolved in AcOH (10 ml) and the solution was refluxed, for 24h. AcOH was evaporated and the residue was dissolved in AcOEt, washed with aqueous NH_4Cl, $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of EtOAc provided the title compound **73** as a brownish powder (297 mg, 95%).

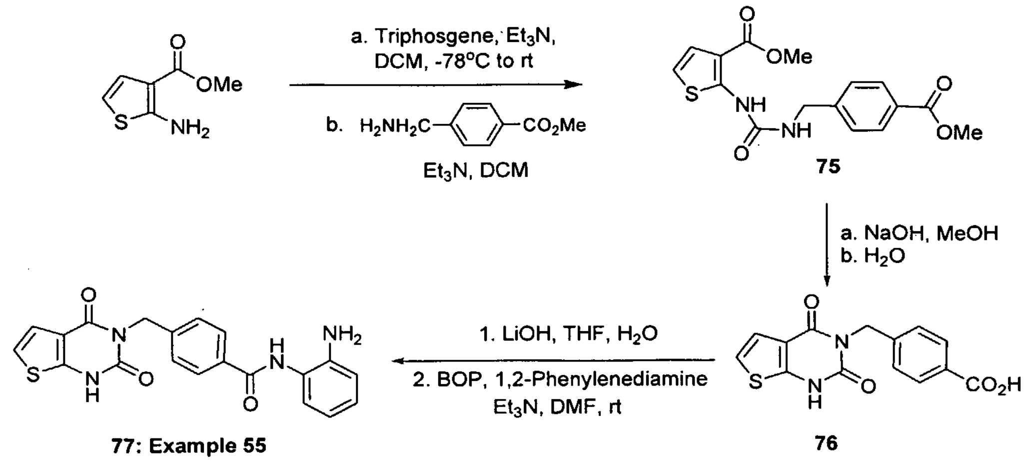
^{1}H NMR (DMSO-d_6) δ (ppm): 7.90 (d, J = 1.8 Hz, 2H), 7.88 (d, J = 1.9 Hz, 1H), 7.66 (d, J = 7 Hz, 1H), 7.51 (d, J = 9.8 Hz, 2H), 4.26 (s, 2H), 3.32 (s, 3H).

LRMS: 318.1 (calc.), 319.4 (obt.)

[0433] Step 3: N-(2-Amino-phenyl)-4-(5-chloro-6-fluoro-1H-benzoimidazol-2-ylmethyl)-benzamide (74).

[0434] Following the procedures described in example 1, steps 4 and 5 the title compound **74** was obtained as a yellow solid (53% yield). ^{1}H NMR: (DMSO) δ (ppm): 9.59 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 6.9 Hz, 1H), 7.51 (d, J = 9.7 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 7.2 Hz, 1H), 6.74 (td, J = 7.6 Hz, 1H), 7.52 (dd, J = 4.7, 4.7 Hz, 1H), 6.57 (dd, J = 7.0, 1.4 Hz, 2H), 4.87 (s, 2H), 4.26 (s, 2H).

Scheme 20

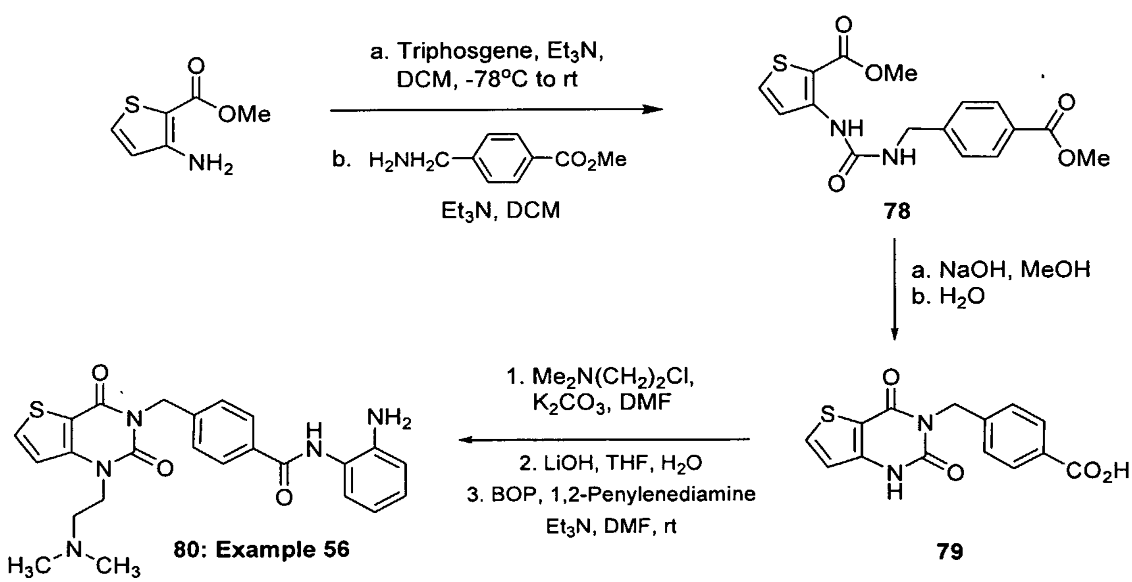


Example 55

N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl)-benzamide (77)

[0435] The title compound 77 was obtained starting from 2-amino-thiophene-3-carboxylic acid methyl ester via the intermediates 75 and 76 (scheme 20) following the same procedures described in Patent Application WO 03/024448 (69% yield). ^{1}H NMR (DMSO) δ (ppm): 9.59 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.18-7.11 (m, 3H), 7.45 (bs, 1H), 6.94 (td, J = 7.6, 1.6 Hz, 1H), 6.75 (dd, J = 7.8, 1.4 Hz, 1H), 6.57 (td, J = 7.5, 1.4 Hz, 1H), 5.09 (s, 2H), 4.87 (bs, 2H). LRMS: 392.1 (calc.), 393.4 (obt.).

Scheme 21

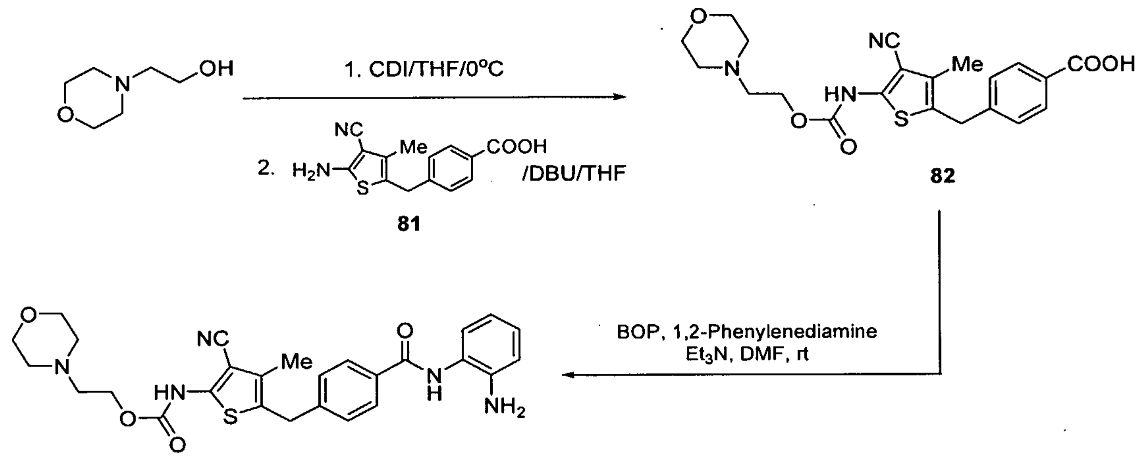


Example 56

N-(2-Amino-phenyl)-4-[1-(2-dimethylamino-ethyl)-2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl]-benzamide (80)

[0436] The title compound 80 was obtained starting from 3-amino-thiophene-2-carboxylic acid methyl ester via the intermediates 78 and 79 as a yellow solid following the same procedures described in the Patent Application WO 03/024448. ^{1}H NMR (DMSO) δ (ppm): 9.60 (s, 1H), 8.22 (d, J = 5.5 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.41-7.39 (m, 3H), 7.13 (d, J = 7.4 Hz, 1H), 6.95 (td, J = 7.6, 1.6 Hz, 1H), 6.75 (dd, J = 7.8, 1.6 Hz, 1H), 6.57 (td, J = 7.4, 1.2 Hz, 1H), 5.16 (s, 2H), 4.88 (bs, 2H), 4.23 (m, 2H), 2.81 (m, 2H). LRMS: 463.2 (calc.), 464.4 (obt.).

Scheme 22



83: Example 57

Example 57

{5-[4-(2-Amino-phenylcarbamoyl)-benzyl]-3-cyano-4-methyl-thiophen-2-yl}-carbamic acid 2-morpholin-4-yl-ethyl ester (83)

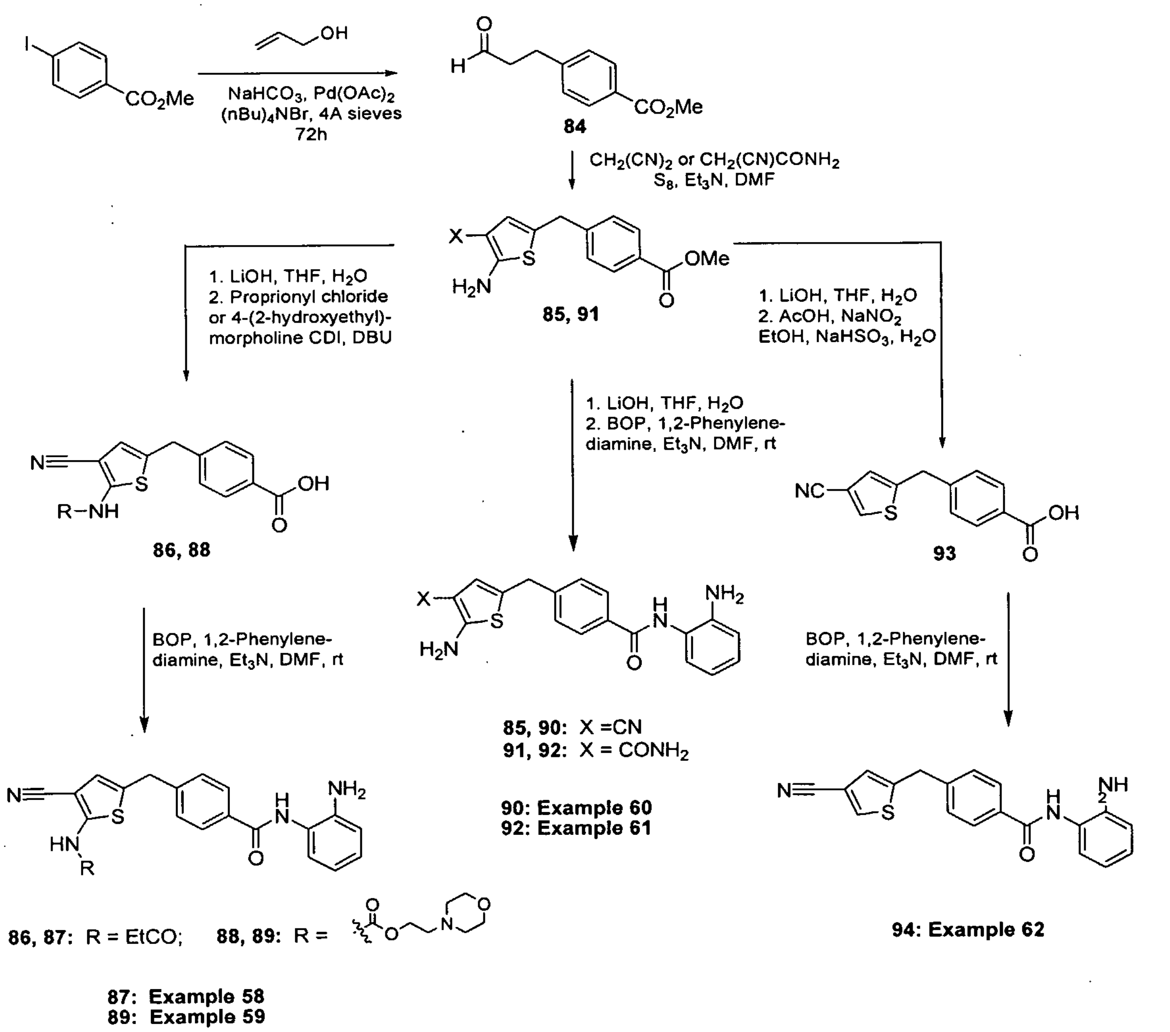
[0437] Step 1: 4-[4-Cyano-3-methyl-5-(2-morpholin-4-yl-ethoxycarbonylamino)-thiophen-2-ylmethyl]-benzoic acid (82)

[0438] To a solution of carbonyl diimidazole (207 mg, 1.28 mM) in anhydrous THF (10 ml) hydroxyethyl morpholine (114 μl, 1.28 mM) was added at 5°C. Cooling was removed, the reaction mixture stirred at rt for 1 hr and added via canula to a solution of 4-(5-amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid (**81**, 350 mg, 1.28 mM) (described in the Patent Application WO 03/024448) and DBU (382 μl, 2.56 mM) in anhydrous THF (20 ml) at rt. The combined mixture stirred 3 hrs, THF was evaporated and the remaining solid residue was suspended in water, acidified with conc. HCl (pH 4) and collected by filtration. Trituration of this material with 25 ml acetone provided the title compound **82** (85 mg, 15% yield). LRMS: 429.5 (calc.) 430.4 (found).

[0439] Step 2: {5-[4-(2-Amino-phenylcarbamoyl)-benzyl]-3-cyano-4-methyl-thiophen-2-yl}-carbamic acid 2-morpholin-4-yl-ethyl ester (83)

[0440] Following the procedure described in example 1, step 5 the title compound **83** was obtained as a solid (26% yield). ^{1}H NMR: (300 MHz, DMSO-d_6, δ (ppm): 9.61 (s, 1H), 7.92 (d, J=7.91, 2H), 7.34 (d, J=7.91, 2H), 7.15 (d, J=7.47, 1H), 6.97 (t, J=7.03, 1H), 6.77 (d, J=7.03, 1H), 6.59 (t, J=7.47, 1H), 4.88 (brs, 2H), 4.22 (t, J=5.50, 2H), 4.10 (s, 2H), 3.55 (t, J=4.40, 4H), 2.56 (t, J=5.50, 2H), 2.43-2.39 (m, 4H), 2.18 (s, 3H). LRMS: 519.6 (calc. 520.5 (found).

Scheme 23



Example 58

N-(2-Amino-phenyl)-4-(4-cyano-5-propionylamino-thiophen-2-ylmethyl)-benzamide (87)

[0441] Step 1: 4-(3-Oxo-propyl)-benzoic acid methyl ester (84).

[0442] The title compound **84** was obtained according to the procedure described in *J. Org. Chem.*; **1992**; *57*(11); 3218-3225, starting from 4-iodobenzoic acid methyl ester.

[0443] Step 2: 4-(5-Amino-4-cyano-thiophen-2-ylmethyl)-benzoic acid methyl ester (85)

[0444] To a suspension of sulfur (309 mg, 4.22 mmol) and methyl 4-(3-oxo-propyl)-benzoate (**84**) (812 mg, 4.22 mmol) in DMF (4 ml) at 0°C was slowly added Et_3N (353 µl, 2.53 mmol) at 0°C. The reaction mixture was stirred 1 h at room temperature and a solution of malononitrile (279 mg, 4.22 mmol) in DMF (6 ml) was slowly added. The reaction mixture was stirred at room temperature for 16 h, poured into 300 ml of ice/water to yield an orange precipitate, which was filtered, rinsed with cold water and dried to afford the title compound **85** (1.04 g, 90%) as an orange solid. LRMS: 272.1 (Calc.); 265.0 (found).

[0445] Steps 3, 4: N-(2-Amino-phenyl)-4-(4-cyano-5-propionylamino-thiophen-2-ylmethyl)-benzamide (87)

[0446] The title compound **87** was obtained starting from the cyano- compound **85** via the intermediate **86** as a yellow solid following the same procedures as described in Patent Application WO 03/024448, for a similar compound (63% yield). ^{1}H NMR (DMSO) δ (ppm): 11.26 (s, 1H), 9.61 (s, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.95 (s, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.58 (m, 1H), 5.76-5.75 (m, 1H), 4.88 (s, 2H), 4.12 (s, 2H), 2.50 (m, 3H), 1.05-1.03 (m, 3H). LRMS: 404.1 (calc.), 405.1 (obt.).

Example 59

{5-[4-(2-Amino-phenylcarbamoyl)-benzyl]-3-cyano-thiophen-2-yl}-carbamic acid 2-morpholin-4-yl-ethyl ester (89)

[0447] The title compound **89** was obtained starting from the cyano compound **85** via the intermediate **88** similarly to the compound **87**, example 58 (scheme 23) as a yellow solid (15% yield). ^{1}H NMR: (300 MHz, DMSO-d_6, δ (ppm): 9.60 (bs, 1H), 7.91 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.8 Hz, 1H), 6.97-6.93 (m, 2H), 6.76(dd, J = 7.8, 1.2 Hz, 1H), 6.58 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 4.89 (bs, 2H), 4.22 (t, J = 5.5 Hz, 2H), 4.12 (s, 2H), 3.55 (t, J = 4.7 Hz, 4H), 2.56 (t, J = 5.7 Hz, 2H), 2.41 (m, 4H).

Example 60

4-(5-Amino-4-cyano-thiophen-2-ylmethyl)-N-(2-amino-phenyl)-benzamide (90)

[0448] The title compound **90** was obtained starting from the compound **85** as an orange solid following the same procedures described in example 1 steps 4 and 5, (67% yield). ^{1}H NMR: (DMSO) δ (ppm): 9.60 (bs, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 6.7 Hz, 1H), 7.03 (bs, 1H), 6.95 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 6.76 (dd, J = 6.6, 1.6 Hz, 1H),

6.58 (ddd, J = 7.4, 7.4, 1.7 Hz, 1H), 6.52 (s, 1H), 4.89 (bs, 2H), 3.95 (s, 2H). LRMS: 348.1 (Calc.); 349.2 (found).

Example 61

2-Amino-5-[4-(2-amino-phenylcarbamoyl)-benzyl]-thiophene-3-carboxylic acid amide (92)

[0449] Step 2: 4-(5-Amino-4-carbamoyl-thiophen-2-ylmethyl)-benzoic acid methyl ester (91)

[0450] The title compound **91** was obtained as a yellow solid by following the same procedure as described in Example 58 step 2 (replacing malononitrile by 2-cyano-acetamide), (88% yield). LRMS: 304.1 (calc.); 305.1 (found).

[0451] Step 3-4: 2-Amino-5-[4-(2-amino-phenylcarbamoyl)-benzyl]-thiophene-3-carboxylic acid amide (92)

[0452] The title compound **92** was obtained as an orange solid starting from the compound **91** and following the same procedures as described in example 1 steps 4 and 5 (54% yield). ^1H NMR: (DMSO) δ (ppm): 9.62(s, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.14-7.12 (m, 3H), 6.95 (td, J = 7.6, 1.6 Hz, 1H), 6.84(s, 1H), 6.76 (dd, J = 7.8, 1.2 Hz, 1H), 6.58 (td, J = 7.4, 1.2 Hz, 1H), 4.87 (s, 2H), 3.93 (s, 2H). LRMS: 366.1 (Calc.); 367.4 (found).

Example 62

N-(2-Amino-phenyl)-4-(4-cyano-thiophen-2-ylmethyl)-benzamide (94)

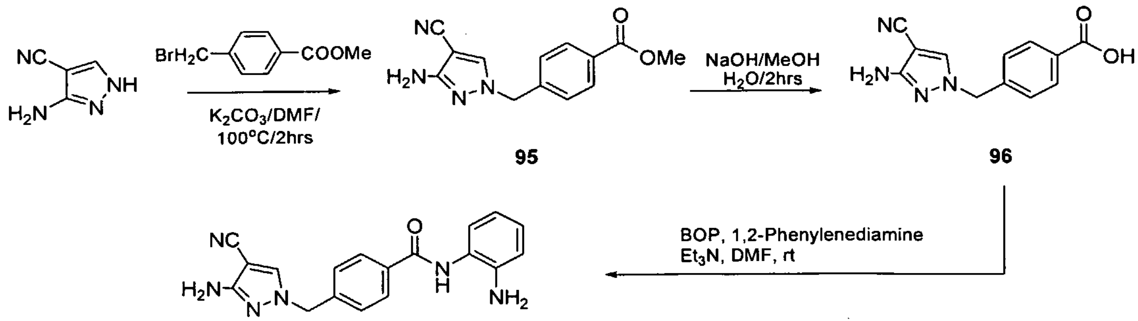
[0453] Step 4: 4-(4-Cyano-thiophen-2-ylmethyl)-benzoic acid (93).

[0454] Starting from the cyano compound **85** and following the procedures described in example 1, step 4 (ester hydrolysis) and a procedure described in *Tetrahedron Lett.;* **2001**; *42*(32); 5367-5370 (de-amination) the title compound **93** was obtained as a brown solid (76% yield). LRMS: 243.1 (calcd.), 244.3 (found).

[0455] Step 5: N-(2-Amino-phenyl)-4-(4-cyano-thiophen-2-ylmethyl)-benzamide (94)

[0456] The title compound **94** was obtained as an orange solid starting from the compound **93** by following the same procedures described in example 1 step 5 (41% yield). ^1H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.38 (d, J = 1.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 1.4 Hz, 1H), 7.13 (d, J = 6.8 Hz, 1H), 6.95 (td, J = 7.6, 1.6 Hz, 1H), 6.75 (dd, J = 8.0, 1.4 Hz, 1H), 6.57 (td, J = 7.4, 1.2 Hz, 1H), 4.89 (bs, 2H), 4.27 (s, 2H). LRMS: 333.1 (Calc.); 334.4 (found).

Scheme 24



97: Example 63

Example 63

4-(3-Amino-4-cyano-pyrazol-1-ylmethyl)-N-(2-amino-phenyl)-benzamide (97)

[0457] Step 1: 4-(3-Amino-4-cyano-pyrazol-1-ylmethyl)-benzoic acid methyl ester (95)

[0458] To a solution of 3-amino-1H-pyrazole-4-carbonitrile (1.211 g, 11.21 mmol) in anhydrous DMF (20 ml) K_2CO_3 (5.414 g, 39.24 mmol) was added. The suspension was stirred 5 min at room temperature and treated with p-bromomethylbenzoic acid methyl ester (2.568 g, 11.21 mmol), stirred for 2.5 hrs at 100°C, cooled and filtered. Filtrate was evaporated to form an oily residue, which was dissolved in a mixture Et_2O-acetone and kept overnight at -10°C. A crystalline material was formed which was triturated with hot EtOAc, again kept overnight at -10°C and was collected by filtration to form the title compound **95** (675 mg, 24% yield). LRMS: 256.3 (calc.), 257.3 (found).

[0459] Step 2: 4-(3-Amino-4-cyano-pyrazol-1-ylmethyl)-benzoic acid (96)

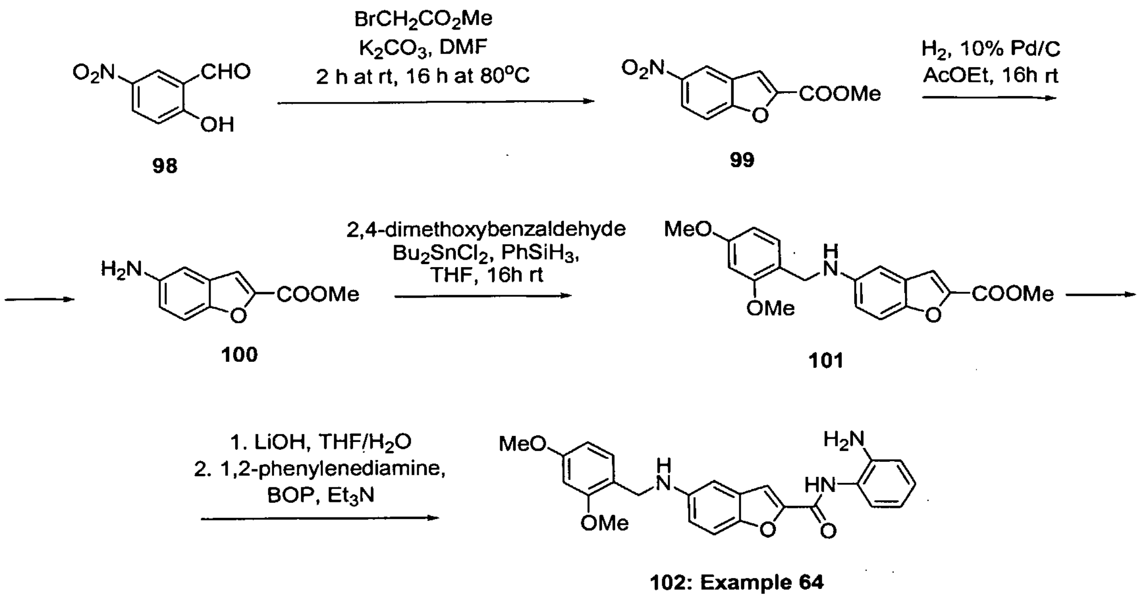
[0460] To a solution of NaOH (343 mg, 8.58 mmol) in a mixture of water (10 ml) and MeOH (20 ml) the ester **95** (732 mg, 2.86 mmol) was added. The reaction mixture was refluxed 2 min and stirred for additional 2 hrs at ambient temperature. MeOH was removed under reduced pressure and remaining aqueous solution was acidified with conc. HCl (pH 3-4) to form a precipitate which was collected by filtration to afford the title compound (**96**) (640 mg, 92% yield). LRMS: 242.2 (calc.), 241.1 (found).

[0461] Step 3: 4-(3-Amino-4-cyano-pyrazol-1-ylmethyl)-N-(2-amino-phenyl)-benzamide (97)

[0462] The title compound 97 was obtained as a white solid starting from the compound 96 following the same procedures as described in example 1 step 5. Crude product was purified by flash chromatography, eluent MeOH-CH_2Cl_2 (2:23) followed by trituration with CH_2Cl_2, to afford the title compound 97 (58% yield). ^{1}H NMR: (400 MHz, DMSO-d_6, δ (ppm): 9.61 (s, 1H), 8.27 (s, 1H), 7.92 (d, J=8.2, 2H), 7.33 (d, J=8.2, 2H), 7.13 (d (dd), J=7.8, 1H), 6.95 (dd, J=1.4 Hz, J = 7.8

Hz, 1H), 6.75 (dd, J = 1.2 Hz, j = 7.8 Hz, 1H), 6.57 (dd, J = 1.2 Hz, 7.6 Hz, 1H), 5.60 (s, 2H), 5.16 (s, 2H), 4.89 (s, 2H). LRMS: 332.4 (calc.), 333.4 (found).

Scheme 25



Example 64

<u>5-(2,4-Dimethoxy-benzylamino)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (102)</u>

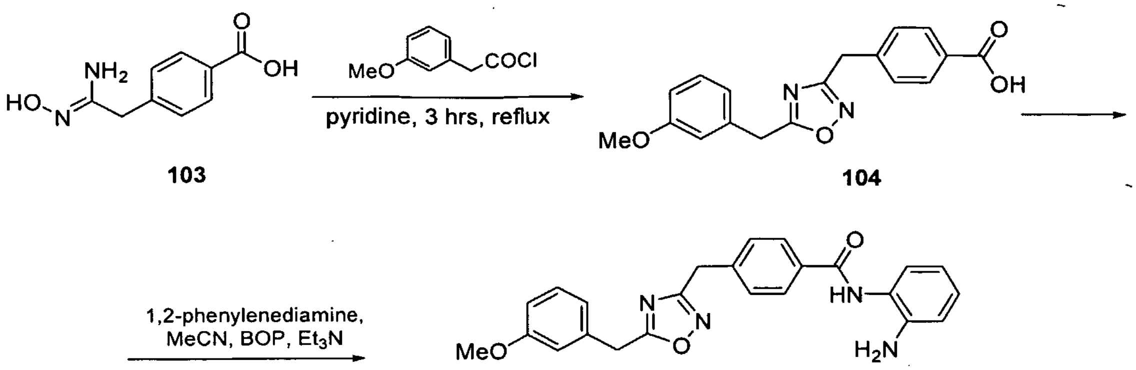
[0463] <u>Steps 1-2: 5-Amino-benzofuran-2-carboxylic acid methyl ester (100)</u>

[0464] The title compound 100 was obtained following the procedures described in *J. Am. Chem. Soc.* 2000, 122, (6382-6394), starting from 2-hydroxy-5-nitro-benzaldehyde (98) via the intermediate ester 99 (74% yield).

[0465] <u>Steps 3-4: 5-(2,4-Dimethoxy-benzylamino)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (102)</u>

[0466] The title compound 102 was obtained as a orange solid via the intermediates 100 and 101 by following the same procedures as described in example 12, step 2 (scheme 3), and example 1, steps 4 and 5 (scheme 1) (76 mg, 41%). ^{1}H NMR: (DMSO) δ (ppm): 9.69 (s, 1H), 7.44 (s, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.17-7.15 (m, 2H), 6.96 (td, J = 7.5, 1.4 Hz, 1H), 6.84 (dd, J = 9.0, 2.3 Hz, 1H), 6.76 (dd, J = 8.0, 2.3 Hz, 1H), 6.67 (d, J = 2.3 Hz, 1H), 6.60-6.56 (m, 2H), 6.45 (dd, J = 8.2, 2.3 Hz, 1H), 5.94 (t, J = 6.0 Hz, 1H), 4.92 (s, 2H), 4.15 (d, J = 5.7 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H). LRMS: 417.2 (calc.); 418.5 (obt.).

Scheme 26



105: Example 65

Example 65

N-(2-Amino-phenyl)-4-[5-(3-methoxy-benzyl)-[1,2,4]oxadiazol-3-ylmethyl]-benzamide (105)

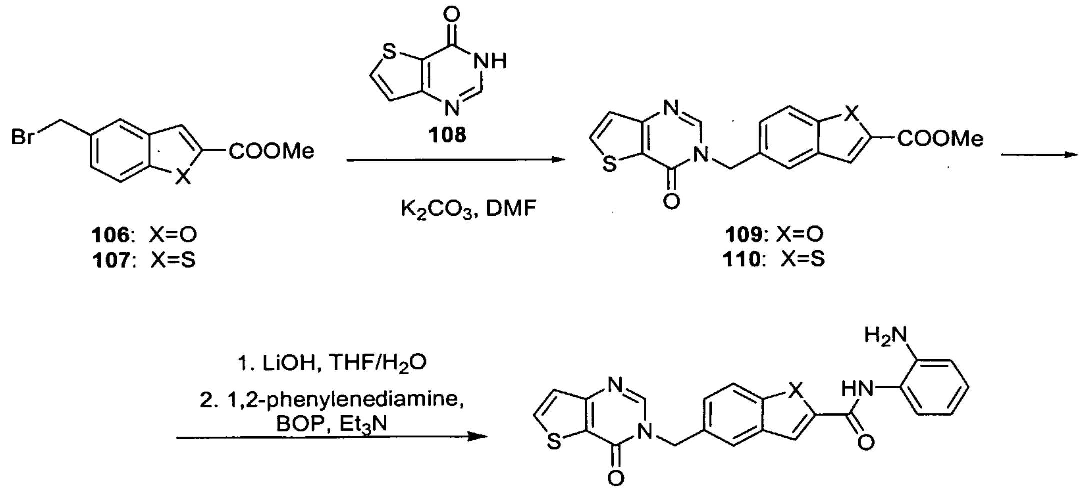
[0467] Step 1. 4-[5-(3-Methoxy-benzyl)-[1,2,4]oxadiazol-3-ylmethyl]-benzoic acid (104)

[0468] To a suspension of 4-(N-hydroxycarbamidoylmethyl)-benzoic acid (**103**) (described in the Patent Application WO 03/024448) (464 mg, 2.40 mmol) in anhydrous pyridine (10 ml) (3-methoxy-phenyl)-acetyl chloride (418 mg, 2.27 mmol) was added and the reaction mixture was refluxed for 3 hrs, cooled, quenched with water (10 ml) and evaporated to form a solid residue. This material was re-dissolved in CH_2Cl_2, decolorized with charcoal and purified 3 times by flash chromatography with the eluents being CH_2Cl_2-MeOH (19:1), CH_2Cl_2-acetone (19:1, then 9:1) and acetone-hexane (3:2), to afford the title compound **104** (96 mg, 13%). LRMS: 324.3 (calcd.), 323.3 $[M-H]^-$ (found).

N-(2-Amino-phenyl)-4-[5-(3-methoxy-benzyl)-[1,2,4]oxadiazol-3-ylmethyl]-benzamide (105)

[0469] The title compound **105** was obtained as a white solid following the same procedures described in example 1 step 5 (scheme 1). The crude product was purified twice by flash chromatography, eluents MeOH-CH_2Cl_2 (1:19), then EtOAc- CH_2Cl_2 (1:2), to afford the title compound in 41% yield. LRMS: 414.5 (calcd.), 415.4 $[MH]^+$ (found). ^1H NMR: (400 MHz, DMSO-d_6, δ (ppm): 9.61 (s, 1H), 7.91 (d, J=8.22, 2H), 7.41 (d, J=8.22, 2H), 7.25 (t, J=7.83, 1H), 7.14 (d, J=6.65, 1H), 6.96 (m, 1H), 6.89-6.84 (m, 3H), 6.76 (dd, J=8.02, 1.37, 1H), 6.58 (dt, J=7.63, 1.30, 1H), 4.89 (s, 2H), 4.29 (s, 2H), 4.16 (s, 2H), 3.73 (s, 3H).

Scheme 27



106: X=O
107: X=S

109: X=O
110: X=S

111: Example 66: (X=O)
112: Example 67: (X=S)

Example 66

5-(4-Oxo-4H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (111)

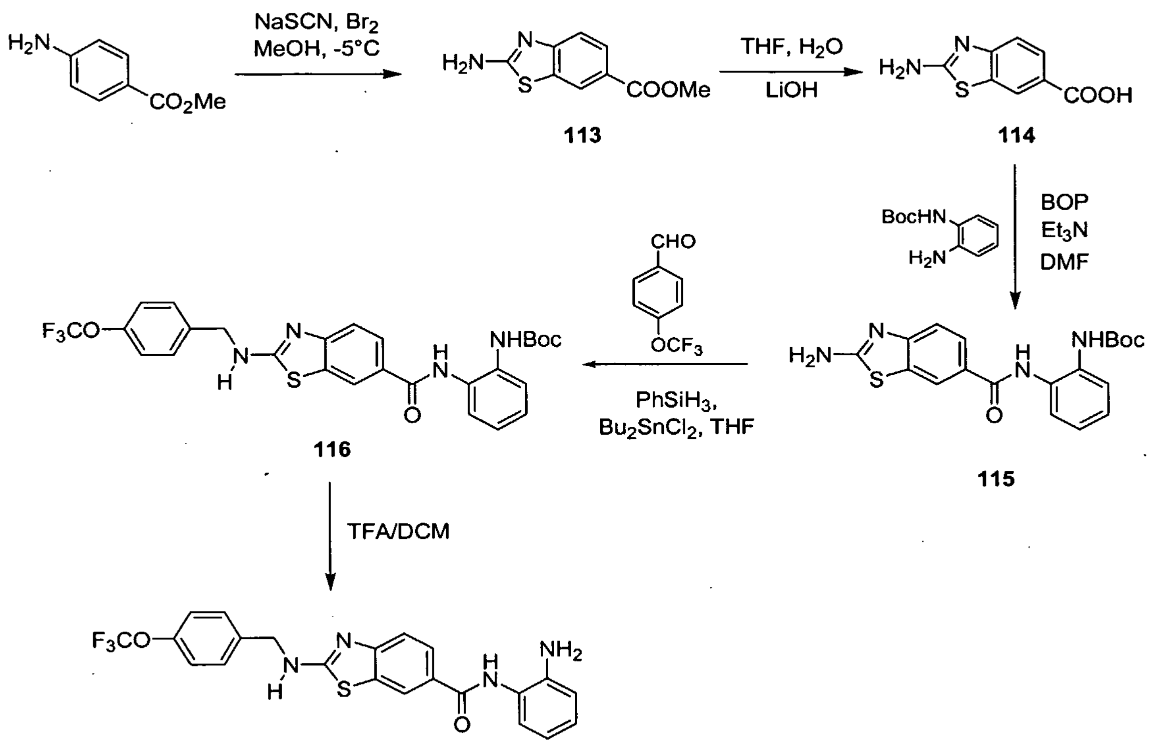
[0470] The title compound **111** was obtained starting from the compound **106** [reacting with 3*H*-thieno[3,2-d]pyrimidin-4-one (**108**)] via the intermediate **109,** following the procedures described in the Patent Application WO 03/024448. ^{1}H NMR: (DMSO) δ (ppm): 9.87 (s, 1H); 8.72 (s, 1H); 8.20 (d, J=5.5 Hz, 1H); 7.81 (s, 1H); 7.68 (m, 2H); 7.54 (dd, J= 8.6, 1.6 Hz, 1H), 7.42 (d, J=5.5 Hz, 1H); 7.17 (d, J=6.6, 1H); 6.98 (dt, J= 7.8, 1.6 Hz, 1H); 6.77 (dd, J= 8.2, 1.6Hz, 1H), 6.59 (dt, J= 7.4, 1.6 Hz, 1H); 5.35 (s, 2H); 4.96 (s, 2H) . LRMS: 416.1 (calc.), 417.4 (obt.).

Example 67

5-(4-Oxo-4H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (112)

[0471] The title compound **112** was obtained starting from the compound **107** [reacting with 3*H*-thieno[3,2-d]pyrimidin-4-one (**108**)] via the intermediate **110,** following the procedures described in the Patent Application WO 03/024448. ^{1}H NMR: (DMSO) δ (ppm): 9.89 (s, 1H), 8.74 (s, 1H), 8.29 (s, 1H), 8.21 (d, J=5.28, 1H), 8.03 (d, J=8.22, 1H), 7.98 (s, 1H), 7.51 (dd, J=8.51, 1.67, 1H), 7.43 (d, J=5.28, 1H), 7.17 (dd, J=7.73, 1.27, 1H), 6.99 (m, 1H), 6.79 (dd, J=8.22, 1.37, 1H), 6.60 (dt, J=7.43, 1.37, 1H), 5.38 (s, 2H), 5.00 (s, 2H). LRMS: 432.1 (calc.), 433.3 (obt.)

Scheme 28



117: Example 68

Example 68

[0472] Step 5: 2-(4-Trifluoromethoxy-benzylamino)-benzothiazole-6-carboxylic acid (2-amino-phenyl)-amide (117)

[0473] Step 1: 2-Amino-benzothiazole-6-carboxylic acid methyl ester (113)

[0474] The title compound was obtained following the procedure described in *J.Med. Chem.* **1997**; *40* (105-111), starting from 4-amino-benzoic acid methyl ester.

[0475] Step 2 : 2-Amino-benzothiazole-6-carboxylic acid (114)

[0476] The title compound **114** was obtained following the procedure described in example 1 step 4 (97% yield). ^{1}H-NMR (DMSO) δ: 12.58 (s, 1H), 8.23 (d, J=1.8 Hz, 1H); 7.85 (s, 2H); 7.78 (dd, J= 8.4, 1.8Hz, 1H); 7.33 (d, J=7.8 Hz, 1H).

[0477] Step 3: {2-[(2-Amino-benzothiazole-6-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (**115**)

[0478] The acid **114** (1.80 g, 9.27 mmol) was combined with (2-amino-phenyl)-carbamic acid tert-butyl ester (2.31 g, 11.1 mmol) and BOP (4.91 g, 11.1 mmol) in DMF. To this solution Et_3N (5.16 ml, 37.1 mmol) was added and the mixture was stirred overnight at room temperature under nitrogen, concentrated *in vacuo* and purified by flash column chromatography (30% hexane/EtOAc). To further purify the product, the mixture was partitioned between EtOAc and

water, organic layer was separated, dried over $MgSO_4$ and evaporated give the title compound **115** (1.84 g, 52%). ^{1}H-NMR (DMSO) δ: 9.72 (s, 1H), 8.66 (m, 1H); 8.22 (d, J=1.8 Hz, 1H); 7.80 (m, 3H); 7.50 (m, 2H); 7.37 (m, 1H); 7.14 (m, 2H); 1.44 (s, 9H).

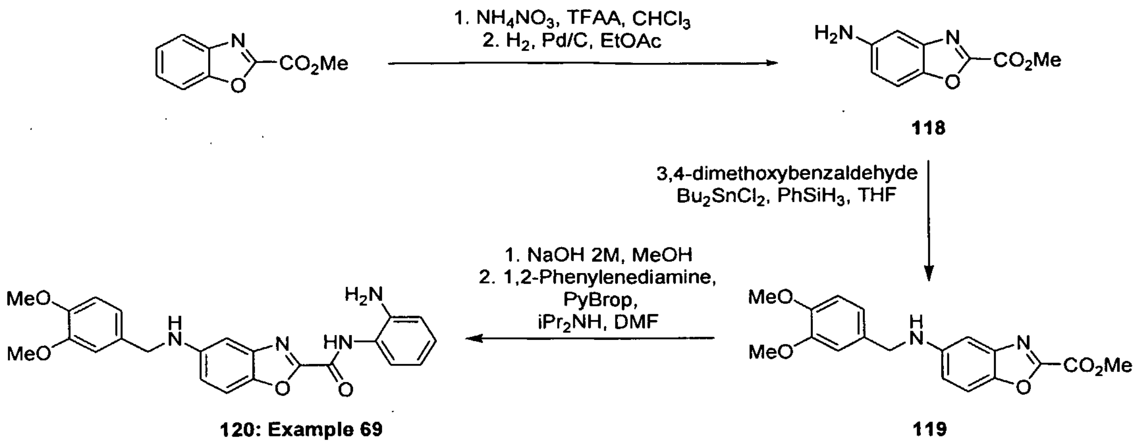
[0479] Step 4: 2-(4-Trifluoromethoxy-phenyl)-benzothiazole-6-carboxylic acid (2-amino-phenyl)-amide (**116**)

[0480] To a solution of **115** (300 mg, 0.78 mmol), 4-(trifluoromethoxy)benzaldehyde (123 μl, 0.86 mmol), and dibutyltin dichloride (24 mg, 0.08 mmol) in THF was added phenylsilane (106 μl, 0.86 mmol). The mixture was stirred overnight at room temperature under nitrogen, additional aldehyde and phenylsilane were added and the stirring continued until no more starting material was present. The THF was evaporated off the mixture and the residue was purified by flash column chromatography (EtOAc/hexane 30/70, then 50/50), to give the title compound **116** (314 mg, 72%). ^{1}H-NMR (DMSO) δ: 9.77 (s, 1H), 8.89 (t, J= 5.7 Hz, 1H); 8.69 (s, 1H); 8.29 (d, J= 1.8 Hz, 1H); 7.84 (dd, J= 8.4, 1.8 Hz, 1H); 7.50 (m, 5H); 7.37 (d, J=7.8 Hz, 2H); 7.17 (m, 2H); 4. 69 (d, J=5.7 Hz, 2H); 1.47 (s, 9H).

[0481] Step 5: 2-(4-Trifluoromethoxy-benzylamino)-benzothiazole-6-carboxylic acid (2-amino-phenyl)-amide (117)

[0482] To a solution of **116** (306 mg, 0.55 mmol) in DCM was added TFA (2.0 ml). This mixture was stirred at room temperature for 4 hours and concentrated. The residue was dissolved in EtOAc, washed with $NaHCO_3$, dried over $MgSO_4$ and concentrated again. The residue was purified by flash column chromatography (30% hexane in EtOAc) to give the title compound **117** as a yellow solid (252 mg, 100%). ^{1}H-NMR (DMSO) δ: 9.56 (s, 1H), 8.83 (t, J=5.8 Hz, 1H), 8.30 (d, J=1.8 Hz, 1H); 7.85 (dd, J= 8.4, 1.6 Hz, 1H); 7.49 (d, J=8.4 Hz, 2H); 7.43 (d, J=8.4 Hz, 1H); 7.34 (d, J=8.4 Hz, 2H); 7.15 (d, J=7.6 Hz. 1H); 6.94 (brt, J= 7.8 Hz, 1H); 6.77 (d, J=7.8 Hz, 1H); 6.59 (t, J=7.5 Hz, 1H); 4.66 (d, J=5.7 Hz, 2H). LRMS: 458.1 (calc.), 459.2 (obt.)

Scheme 29



Example 69

6-(3,4-Dimethoxy-benzylamino)-benzooxazole-2-carboxylic acid (2-amino-phenyl)-amide (120)

[0483] Step 1: 5-Amino-benzooxazole-2-carboxylic acid methyl ester (118).

[0484] The title compound **118** was obtained following the procedures described in *J. Am. Chem. Soc.* **2000**; *122* (6382-6394) starting from benzooxazole-2-carboxylic acid methyl ester.

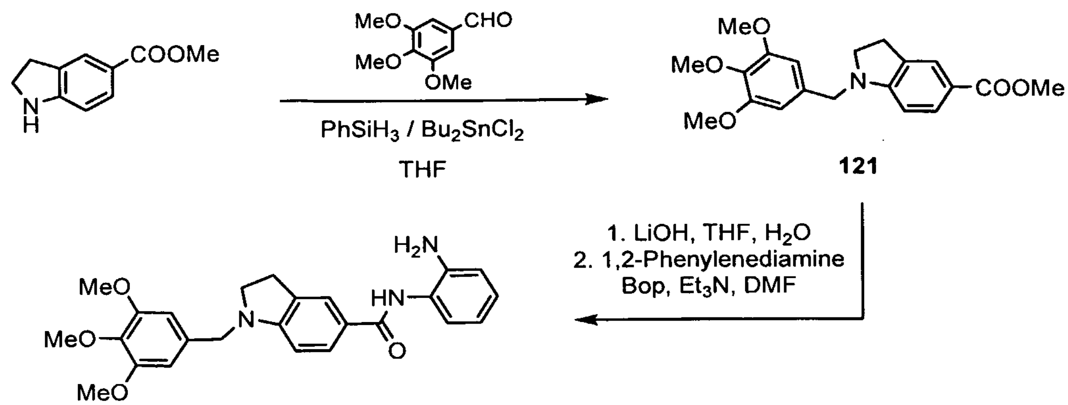
[0485] Step 2: 5-(3,4-Dimethoxy-benzylamino)-benzooxazole-2-carboxylic acid methyl ester (119)

[0486] The title compound **119** was obtained as a solid following the same procedure as described in example 68 step 4 (scheme 28) (90% yield). LRMS: 342.1 (Calc.); 343.4 (found).

[0487] Steps 4-5: 6-(3,4-Dimethoxy-benzylamino)-benzooxazole-2-carboxylic acid (2-amino-phenyl)-amide (120)

[0488] The title compound **120** was obtained following the procedures described in example 1, step 5 (scheme 1) (31% yield). ^{1}H NMR: (DMSO) δ (ppm): 10.06 (s, 1H), 7.56 (d, J=8.80, 1H), 7.22 (dd, J=7.83, 1.37, 1H), 7.02 (d, J=1.57, 1H), 6.98 (m, 1H), 6.92 (d, J=1.76, 1H), 6.88 (d, J=1.96, 1H), 6.86 (d, J=2.35, 1H), 6.82 (d, J=1.96, 1H), 6.78 (dd, J=7.93, 1.27, 1H), 6.60 (m, 1H), 4.99 (brs, 2H), 4.28 (d, J=5.48, 2H), 3.76 (s, 3H), 3.73 (s, 3H). LRMS: 418 (calc.), 419.5 (obt.).

Scheme 30



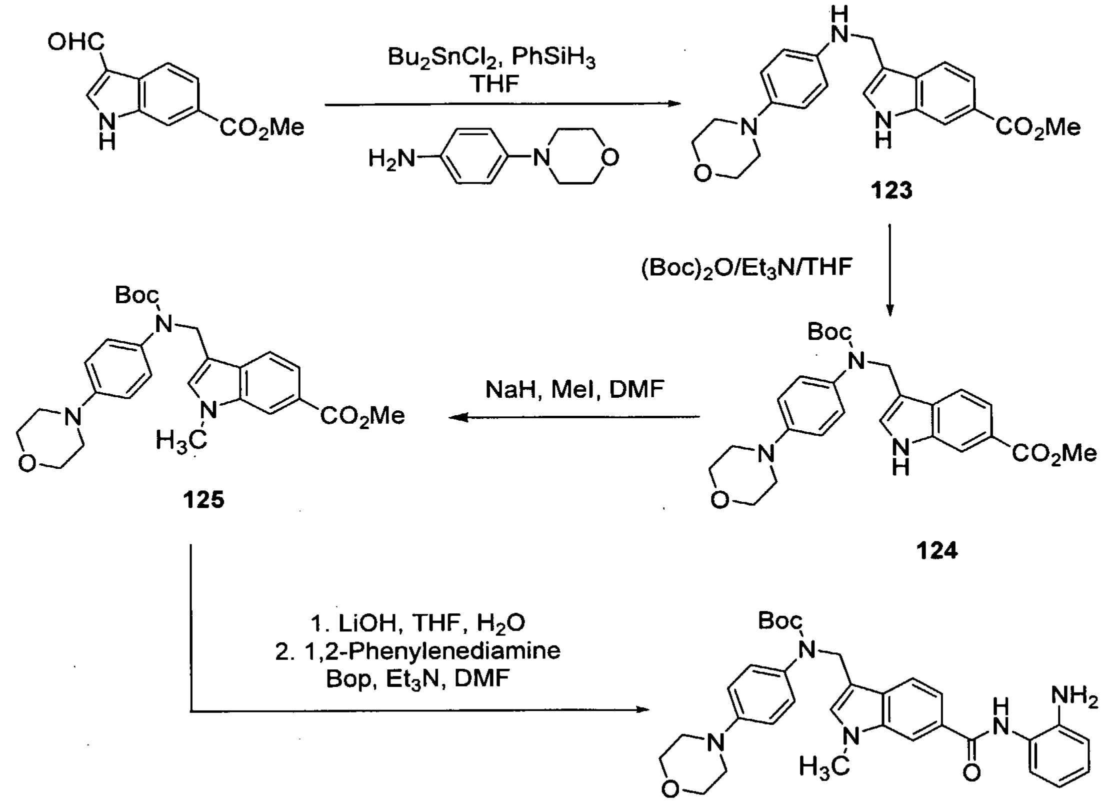
122: Example 70

Example 70

1-(3,4,5-Trimethoxy-benzyl)-2,3-dihydro-1H-indole-5-carboxylic acid (2-amino-phenyl)-amide (122)

[0489] The title compound **122** was obtained following the procedure described in example 68 step 4 (scheme 28) (to produce the intermediate **121**) and procedures described in example 1, steps 4 and 5 (scheme 1) (33% yield). ^{1}H-NMR (DMSO) δ: 9.29 (s, 1H), 7.71 (dd, J=8.22, 1.77, 1H), 7.66 (brm, 1H), 7.12 (dd, J=7.93, 1.47, 1H), 6.93-6.89 (m, 3H), 6.84 (dd, J=8.22, 1.96, 1H), 6.75 (dd, J=8.02, 1.37, 1H), 6.65 (d, J=8.41, 1H), 6.57 (dt, J=7.53, 1.30, 1H), 4.82 (s, 2H), 3.73 (s, 6H), 3.41 (t, J=8.51, 2H), 2.98 (t, J=8.51, 2H). LRMS: 435.2 (Calc.); 436.5 (found).

Scheme 32



126: Example 71

Example 71.

[6-(2-Amino-phenylcarbamoyl)-1-methyl-1H-indol-3-ylmethyl]-(4-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (126)

[0490] Step 1: 3-[(4-Morpholin-4-yl-phenylamino)-methyl]-1H-indole-6-carboxylic acid methyl ester (123)

[0491] To a solution of 3-formyl-1*H*-indole-6-carboxylic acid methyl ester (500 mg, 2.46 mmol), 4-morpholinoaniline (482.3 mg, 2.71 mmol) and dibutyltin dichloride (76 mg, 0.25 mmol) in THF was added phenylsilane (334 μl, 2.71 mmol). The mixture was stirred at room temperature overnight under nitrogen, THF was evaporated off the mixture and the residue was purified by flash chromatography (hexane/EtOAc, 20/80) to afford the title compound **123** (881 mg, 98%). ^{1}H-NMR (DMSO) δ: 8.00 (d, J= 1.0 Hz, 1H), 7.70 (d, J= 8.2 Hz, 1H); 7.58 (dd, J= 8.4, 1.6 Hz, 1H); 7.52 (d, J=2.0 Hz, 1H); 6.70 (d, J= 9.0 Hz, 2H); 6.59 (d, J= 9.0 Hz, 2H); 5.48 (t, J= 5.8 Hz, 1H); 4.31 (d, J=5.7 Hz, 2H); 3.83 (s, 3H); 3.68 (t, J=4.7 Hz, 4H); 2.86 (t, J=4.7 Hz, 4H).

[0492] Step 2: 3-{[tert-Butoxycarbonyl-(4-morpholin-4-yl-phenyl)-amino]-methyl}-1H-indole-6-carboxylic acid methyl ester (124).

[0493] To a solution of 123 (689 mg, 1.89 mmol) in THF (100 ml) Et_3N (289 µl, 2.08 mmol) was added dropwise. $(BOC)_2O$ was added slowly and the mixture was stirred at room temperature overnight under nitrogen, THF was evaporated off and the residue was partitioned between water and CH_2Cl_2. Organic layer was separated, dried over $MgSO_4$, evaporated to form another residue which was purified by flash column chromatography (EtOAc/hexane, 7:3) to afford the title compound 124 (692 mg, 79%). ^{1}H-NMR ($CDCl_3$) δ: 8.24 (m, 1H), 8.09 (m, 1H); 7.76 (dd, J= 8.2, 1.4 Hz, 1H); 7.55 (d, J=8.8 Hz, 1H); 7.13 (d, J=2.5 Hz, 1H); 6.93 (m, 3H); 4.97 (s, 2H); 3.94 (s, 3H); 3.89 (m, 4H); 3.16 (m, 4H); 1.47 (s, 9H).

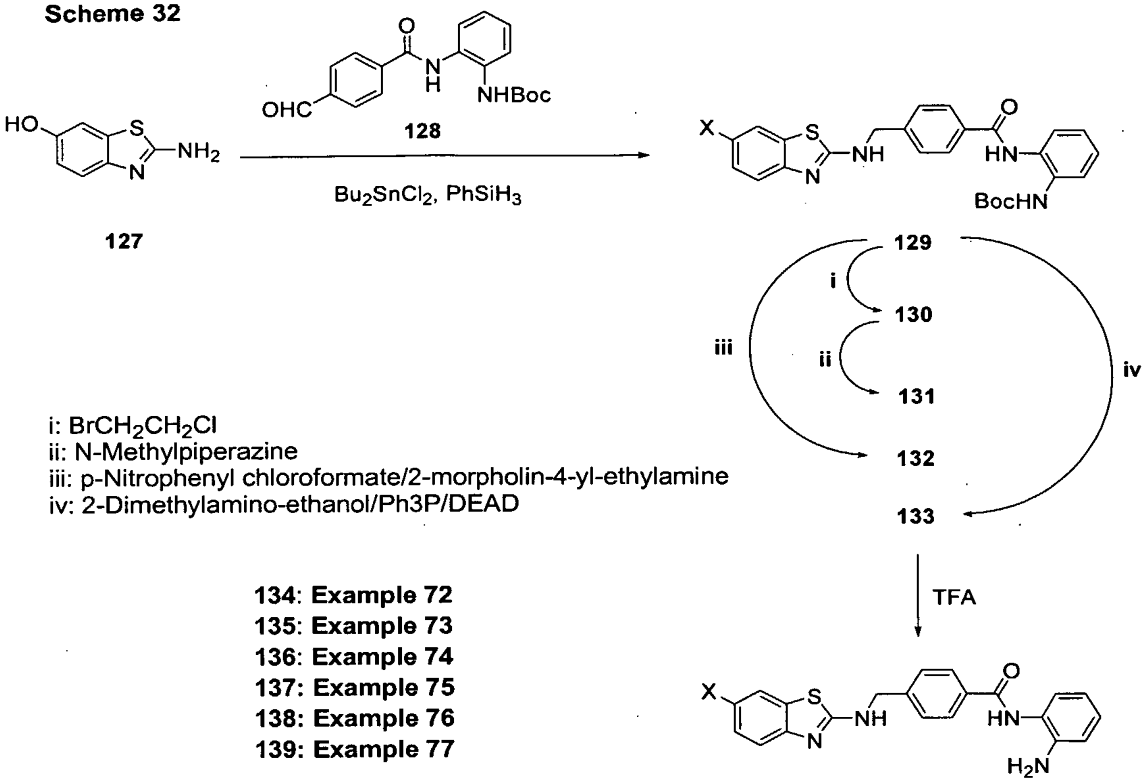
[0494] Step 3: 3-{[tert-Butoxycarbonyl-(4-morpholin-4-yl-phenyl)-amino]-methyl}-1-methyl-1H-indole-6-carboxylic acid methyl ester (125)

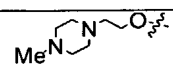
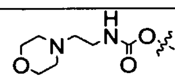
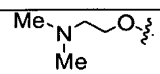
[0495] To a solution of the ester 124 (473 mg, 1.02 mmol) in DMF (15 ml) was added 60% NaH (45 mg, 1.12 mmol). The solution was stirred for one hour at room temperature under nitrogen, cooled to 0°C, treated with MeI (170 µl, 1.12 mmol), warmed to room temperature and stirred overnight under nitrogen. The mixture was partitioned between water and AcOEt, organic layer was collected, dried over $MgSO_4$ and concentrated *in vacuo* to yield 454 mg (93%). ^{1}H-NMR (DMSO) δ: 7.99 (m, 1H), 7.56 (dd, J=1.4, 8.2 Hz, 1H); 7.47 (m, 1H); 7.27 (s, 1H); 6.86 (d, J=8.8 Hz, 2H); 6.75 (d, J=9.0 Hz, 2H); 4.86 (s, 2H); 3.83 (s, 3H); 3.76 (s, 3H); 3.67 (t, J=4.8 Hz, 4H); 3.01 (t, J=4.8 Hz, 4H); 1.37 (s, 9H).

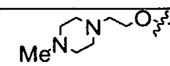
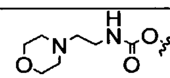
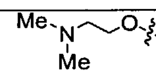
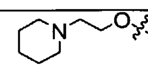
[0496] Steps 4-5: [6-(2-Amino-phenylcarbamoyl)-1-methyl-1H-indol-3-ylmethyl]-(4-morpholin-4-yl-phenyl)-carbamic acid tert-butyl ester (126)

[0497] The procedures described in example 1 steps 4 and 5 (scheme 1) were followed to afford the title compound 126 as a solid (134 mg, 33%). ^{1}H-NMR (DMSO) δ: 9.59 (s, 1H); 8.06 (s, 1H); 7.61 (dd, J=1.6, 8.4 Hz, 1H); 7.48 (m, 1H); 7.21 (s, 1H); 7.15 (dd, J= 7.8, 1.4 Hz, 1H); 6.94 (dt, J= 7.8, 1.6 Hz, 1H); 6.86 (m, 2H); 6.76 (m, 3H); 6.58 (dt, J= 7.4, 1.4 Hz, 1H); 4.88 (s, 2H); 4.87 (s, 2H); 3.76 (s, 3H); 3.68 (t, J=4.8 Hz, 4H); 3.02 (t, J=4.8 Hz, 4H); 1.39 (s, 9H). LRMS: 556.2 (Calc.); 557.5 (found).

Scheme 32



Compound	Ex	X
129		OH
130		OCH_2CH_2Cl
131		
132		
133		
134	72	OH

Compound	Ex	X
135	73	OCH_2CH_2Cl
136	74	
137	75	
138	76	
139	77	

Example 72

_N_-(2-Amino-phenyl)-4-[(6-hydroxy-benzothiazol-2-ylamino)-methyl]-benzamide (134)

[0498] Step 1: (2-{4-[(6-Hydroxy-benzothiazol-2-ylamino)-methyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (129):

[0499] The title compound **129** was obtained following the same procedure as for the reductive amination decribed in Scheme 3, step 2 (example 12) starting from aminothiazole **127** and aldehyde **128** (described in the Patent Application WO 03/024448) (96% yield). ^{1}H NMR: (acetone-d_6) δ(ppm): 9.60 (s, 1H), 8.25 (bs, 1H), 7.99 (d, J= 8.2 Hz, 2H), 7.69 (d, J= 7.4 Hz,

1H), 7.61-7.58 (m, 3H), 7.39 (bs, 1H), 7.27 (d, J= 8.6 Hz, 1H), 7.19 (quint.d, J= 7.4, 2.0 Hz, 2H), 7.12 (d, J= 2.3 Hz, 1H), 6.79 (dd, J= 8.6, 2.7 Hz, 1H), 4.78 (s, 2H), 1.48 (s, 9H). m/z: 491.5 (MH^+).

[0500] Step 2: N-(2-Amino-phenyl)-4-[(6-hydroxy-benzothiazol-2-ylamino)-methyl]-benzamide (134)

[0501] The title compound **134** was obtained starting from compound **129** following the same procedure as for the Boc cleavage decribed in scheme 28, step 5 (example 68) (53% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.58 (s, 1H), 9.12 (s, 1H), 8.25 (t, J= 6.3 Hz, 1H), 7.91 (d, J= 7.8 Hz, 2H), 7.45 (d, J= 8.2 Hz, 2H), 7.15 (d, J= 8.6 Hz, 1H) 7.12 (s, 1H), 7.02 (d, J= 2.7 Hz, 1H), 6.94 (t, J= 6.7 Hz, 1H), 6.75 (dd, J= 8.2, 1.2 Hz, 1H), 6.63 (dd, J= 8.6, 2.3 Hz, 1H), 6.56 (t, J= 7.8 Hz, 1H), 4.87 (s, 2H), 4.59 (d, J= 5.5 Hz, 2H). m/z: 391.2 (MH^+).

Example 73

N-(2-Amino-phenyl)-4-{[6-(2-chloro-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide (135)

[0502] Step 1: [2-(4-{[6-(2-Chloro-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (130):

[0503] The title compound **130** was obtained following the procedure described in *J.Med.Chem.*, **2002**, *45* (6), 1300-1312, and using compound **129** as starting material. (43% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.59 (bs, 1H), 8.25 (bs, 1H), 7.99 (d, J= 8.0 Hz, 2H), 7.69 (dd, J= 7.4, 1.4 Hz, 1H), 7.60 (d, J= 8.4 Hz, 2H), 7.35 (d, J= 8.4 Hz, 1H), 7.32 (d, J= 2.5 Hz, 1H), 7.19 (quint.d, J= 7.2, 2.3 Hz, 2H), 6.91 (dd, J= 8.6, 2.5 Hz, 1H), 4.79 (s, 2H), 4.30 (t, J= 5.3 Hz, 2H), 3.92 (t, J= 5.5 Hz, 3H), 1.48 (s, 9H). m/z: 553.5, 554.5 (M^+, M+1).

[0504] Step 2. N-(2-Amino-phenyl)-4-{[6-(2-chloro-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide (135)

[0505] The title compound **135** was obtained starting from compound **130** following the same procedures as for the Boc cleavage described in scheme 28, step 5 (example 68) (48% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.59 (s, 1H), 8.39 (t, J= 5.5 Hz, 1H), 7.92 (d, J= 8.0 Hz, 2H), 7.46 (d, J= 8.2 Hz, 2H), 7.35 (d, J= 2.5 Hz, 1H), 7.27 (d, J= 8.8 Hz, 1H), 7.13 (d, J= 6.8 Hz, 1H), 6.94 (td, J= 8.0, 1.4 Hz, 1H), 6.83 (dd, J= 8.8, 6.1 Hz, 1H), 6.75 (dd, J= 8.0, 1.4 Hz, 1H), 6.57 (t, J= 8.6 Hz, 1H), 4.88 (s, 2H), 4.63 (d, J= 6.1 Hz, 2H), 4.21 (t, J= 5.1 Hz, 2H), 3.92 (t, J= 5.3 Hz, 2H). mz: 453.4, 455.4 (M^+, M+1).

Example 74

N-(2-Amino-phenyl)-4-({6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-benzothiazol-2-ylamino}-methyl)-benzamide (136)

[0506] Step 1: {2-[4-({6-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-benzothiazol-2-ylamino}-methyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (131):

[0507] The title compound **131** was obtained following the procedure described in *J.Med.Chem.*, **2002**, *45*, (6), 1300-1312, and using compound **130** as starting material. (91% yield). ^{1}H NMR: (Acetone-d_6) δ(ppm): 7.99 (d, J= 8.2 Hz, 2H), 7.69 (d, J= 7.2 Hz, 1H), 7.59 (d, J= 8.6 Hz, 2H), 7.56 (d, J= 2.0 Hz, 1H), 7.33 (d, J= 8.8 Hz, 1H), 7.28 (d, J= 2.5 Hz, 1H), 7.21 (quint.d, J= 7.2, 1.2 Hz, 2H), 7.03-6.93 (m, 1H), 6.87 (dd, J= 8.8, 2.7 Hz, 1H), 4.79 (s, 2H), 4.11 (t, J= 5.9 Hz, 2H), 2.75 (t, J= 5.7 Hz, 2H), 2.67-2.51 (m, 4H), 2.48-2.38 (m, 4H), 2.21 (s, 3H), 1.49 (s, 9H).

[0508] Step 2: N-(2-Amino-phenyl)-4-({6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-benzothiazol-2-ylamino}-methyl)-benzamide (136)

[0509] The title compound **136** was obtained starting from compound **131** following the same procedures as for the Boc cleavage described in scheme 28, step 5 (example 68) (60% yield). ^{1}H NMR: ($CDCl_3$) δ(ppm): 7.97 (d, J= 7.9 Hz, 2H), 7.58 (d, J= 7.9 Hz, 2H), 7.51 (d, J= 8.8 Hz, 1H), 7.42 (d, J= 8.0 Hz, 1H), 7.22-7.17 (m, 2H), 6.99-6.92 (m, 3H), 4.78 (s, 2H), 4.20-4.18 (m, 2H), 2.97-2.87 (m, 8H), 2.70-2.66 (m, 2H), 2.61 (s, 3H). m/z: 517.5 (MH^+).

Example 75

(2-Morpholin-4-yl-ethyl)-carbamic acid 2-[4-(2-amino-phenylcarbamoyl)-benzylamino]-benzothiazol-6-yl ester (137)

[0510] Step 1: [2-(4-{[6-(2-Morpholin-4-yl-ethylcarbamoyloxy)-benzothiazol-2-ylamino]-methyl}-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (132):

[0511] To a solution of *p*-nitrophenylchloroformate (171mg, 0.848mmol) in THF (15 mL) cooled to -78°C under N_2 atmosphere was added Et_3N (236μL, 1.70 mmol). Then a suspension of the intermediate **129** (416mg, 0.848 mmol) in THF (4.2 mL) was added *via canula*. The resulting yellow mixture was stirred at -78°C for 1h and at 0°C for 1.5h, heated at 40°C for 16h and cooled to r.t. Then, neat 4-(2-aminoethyl)morpholine (119 μL, 0.848 mmol) was added and the solution was stirred for 4h, quenched by addition of MeOH. It was allowed to stir for 30 min. and concentrated. The resulting material was purified by flash chromatography using MeOH/DCM (3:97) affording the title compound **132** (165mg, 30% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.77 (s, 1H), 8.64 (bs, 1H), 8.56 (t, J= 5.9 Hz, 1H), 7.90 (d, J= 8.2 Hz, 2H), 7.60 (t, J= 5.9 Hz, 1H),

7.50 (d, J= 8.0 Hz, 2H), 7.50-7.48 (m, 2H), 7.45 (d, J= 2.3 Hz, 1H), 7.30 (d, J= 8.8 Hz, 1H), 7.17 (t, J= 7.6 Hz, 1H), 7.12 (t, J= 7.8 Hz, 1H), 6.90 (dd, J= 8.2, 2.0 Hz, 1H), 4.67 (d, J= 6.0 Hz, 2H), 3.56 (t, J= 4.1 Hz, 4H), 3.31 (t, J= 6.1 Hz, 2H), 3.16 (q, J= 6.1 Hz, 2H), 2.39 (t, J= 6.8 Hz, 4H), 1.42 (s, 9H). m/z: 647.7 (MH^+).

[0512] Step 2: (2-Morpholin-4-yl-ethyl)-carbamic acid 2-[4-(2-amino-phenylcarbamoyl)-benzylamino]-benzothiazol-6-yl ester (137)

[0513] The title compound **137** was obtained starting from compound **132** following the same procedure as for the Boc cleavage described in scheme 28, step 5 (example 68) (55% yield). ^{1}H NMR: (DMSO-d_6): ^{1}H NMR: (DMSO-d_6): 9.60 (s, 1H), 8.56 (t, J= 6.3 Hz, 1H), 7.93 (d, J= 8.4 Hz, 2H), 7.61 (t, J= 5.5 Hz, 1H), 7.47 (d, J= 7.8 Hz, 2H), 7.46 (d, J= 2.3 Hz, 1H), 7.31 (d, J= 8.6 Hz, 1H), 7.14 (d, J= 6.8 Hz, 2H), 6.95 (t, J= 6.5 Hz, 1H), 6.92 (dd, J= 8.8, 2.5 Hz, 1H), 6.75 (d, J= 7.8 Hz, 1H), 6.57 (t, J= 7.4 Hz, 1H), 4.88 (s, 2H), 4.66 (d, J= 5.9 Hz, 2H), 3.57 (t, J= 4.5 Hz, 4H), 3.33-3.31 (m, 2H), 2.41-2.38 (m, 6H). m/z: 547.5 (MH^+).

Example 76

N-(2-Amino-phenyl)-4-{[6-(2-dimethylamino-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide (138)

[0514] Step 1: [2-(4-{[6-(2-Dimethylamino-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (133):

[0515] To a suspension of compound **129** (1.00g, 2.04 mmol) in THF (6.8 mL) at room temperature under N_2 atmosphere were successively added *N,N*-dimethylethanolamine (225 µL, 2.24 mmol) and triphenylphosphine (696 mg, 2.65 mmol) followed by diisopropyl azodicarboxylate (550 µL, 2.65 mmol). Heat was evolved and the mixture turned dark red. It was stirred for 4 h, THF was removed *in vacuo* and the dark residue was partitioned between EtOAc and H_2O. Organic phase was collected and extracted with HCl 1N. Acidic extract was separated and neutralized with saturated aqueous $NaHCO_3$ under vigorous stirring. A white precipitate was formed which was collected by filtration to afford the title compound **133** (430 mg, 37% yield). ^{1}H NMR: (acetone-d_6) δ(ppm): 7.99 (d, J =8.4 Hz, 2H), 7.70 (dd, J= 8.0, 2.2 Hz, 1H), 7.59 (d, J= 8.4 Hz, 2H), 7.56 (d, J= 1.6 Hz, 1H), 7.33 (d, J= 9.0 Hz, 1H), 7.27 (d, J= 2.5 Hz, 1H), 7.19 (quint.d, J= 7.8, 2.4 Hz, 2H), 6.87 (dd, J= 8.8, 2.5 Hz, 1H), 4.80 (s, 2H), 4.08 (t, J= 5.9 Hz, 2H), 2.67 (t, J= 5.7 Hz, 2H), 2.27 (s, 6H), 1.48 (s, 9H). m/z: 562.5 (MH^+).

[0516] Step 2: N-(2-Amino-phenyl)-4-{[6-(2-dimethylamino-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide (138)

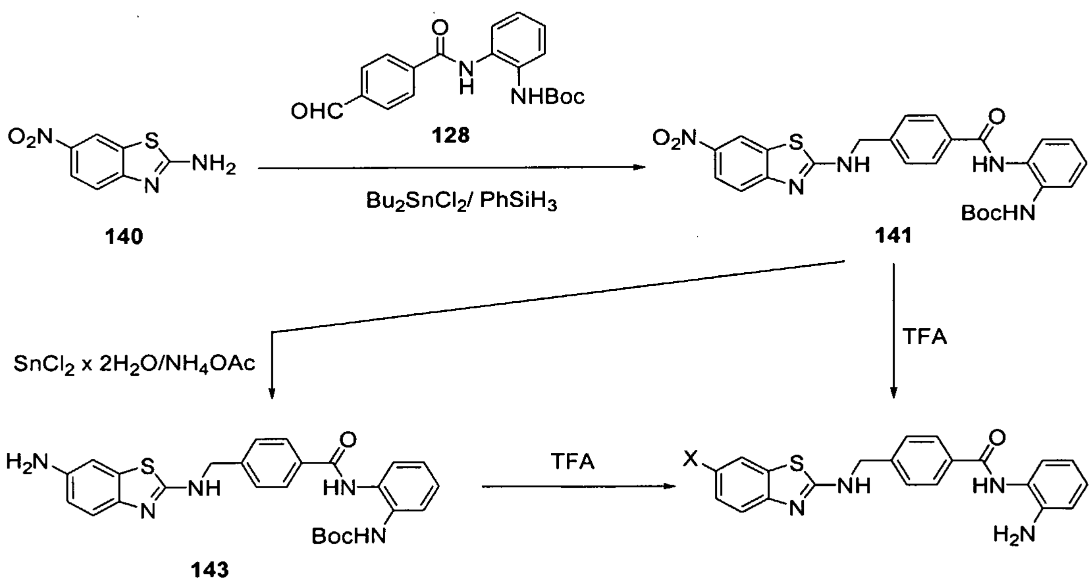
[0517] The title compound **138** was obtained starting from the compound **133** following the same procedures as for the Boc cleavage described in scheme 28, step 5 (example 68) (82% yield). ^{1}H NMR: (CD_3OD) δ(ppm): 7.96 (d, J= 8.2 Hz, 2H), 7.53 (d, J= 8.2 Hz, 2H), 7.32 (d, J= 8.8 Hz, 1H), 7.23 (d, J= 2.5 Hz, 1H), 7.17 (d, J= 9.0 Hz, 1H), 7.07 (td, J= 9.0, 1.6 Hz, 1H), 6.90(dd, J= 8.8, 2.7 Hz, 1H), 6.89 (dd, J= 6.5, 1.6 Hz, 1H), 6.76 (t, J= 6.5 Hz, 1H), 4.71 (s, 2H), 4.10 (t, J= 5.3 Hz, 2H), 2.79 (t, J= 5.5 Hz, 2H), 2.36 (s, 6H). m/z: 462.5 (MH^+).

Example 77

_N_-(2-Amino-phenyl)-4-{[6-(2-piperidin-1-yl-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide (139)

[0518] The title compound **139** was obtained following the same procedures (two-step reaction sequence) described in example 76 but substituting *N,N*-dimethylethanolamine for 1-piperidineethanol (52% yield over two steps). ^{1}H NMR: (CD_3OD) δ(ppm): 7.96 (d, J= 8.4 Hz, 2H), 7.53 (d, J= 8.2 Hz, 2H), 7.36 (d, J= 8.8 Hz, 1H), 7.32 (d, J= 2.5 Hz, 1H), 7.17 (d, J= 8.0 Hz, 1H), 7.07 (td, J= 6.1, 1.2 Hz, 1H), 6.97 (dd, J =8.8, 2.7 Hz, 1H), 6.90 (d, J= 7.8 Hz, 1H), 6.77 (t, J= 7.2 Hz, 1H), 4.71 (s, 2H), 4.35 (t, J= 4.9 Hz, 2H), 3.64-3.60 (m, 2H), 3.56 (t, J= 4.9 Hz, 2H), 3.10-3.01 (m, 2H), 2.05-1.92 (m, 2H), 1.90-1.81 (m, 4H). m/z: 502.5 (MH^+).

Scheme 33



142: **Example 78** (X= NO_2)
144: **Example 79** (X= NH_2)

Example 78

N-(2-Amino-phenyl)-4-[(6-nitro-benzothiazol-2-ylamino)-methyl]-benzamide (142)

[0519] Step 1: (2-{4-[(6-Nitro-benzothiazol-2-ylamino)-methyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (141):

[0520] The title compound **141** was obtained starting from compounds **140** and **128** (described in the Patent Application WO 03/024448), following the same procedure as for the reductive amination described in scheme 3, step 2 (example 12) (66% yield). ^{1}H NMR: (CD_3OD) δ(ppm): 9.78 (s, 1H), 9.28 (bs, 1H), 8.71 (d, J= 2.5 Hz, 1H), 8.64 (bs, 1H), 8.09 (dd, J= 9.0, 2.5 Hz, 1H), 7.92 (d, J= 8.2 Hz, 2H), 7.51 (dd, J= 8.6, 2.2 Hz, 2H), 7.46 (d, J= 9.0, 2H), 7.17 (td, J= 7.4, 1.8 Hz, 1H), 7.12 (td, J= 7.1, 1.8 Hz, 1H), 4.75 (bs, 2H), 1.42 (s, 9H). m/z: 542.2 (M+Na).

[0521] Step 2: N-(2-Amino-phenyl)-4-[(6-nitro-benzothiazol-2-ylamino)-methyl]-benzamide (142)

[0522] The title compound **142** was obtained following the same procedure as for the Boc cleavage described in scheme 28, step 5 (example 68) using compound **141** as the starting material (98% yield). ^{1}H NMR: (DMSO-d_6): 10.06 (s, 1H), 9.30 (bs, 1H), 8.71 (d, J= 2.3 Hz, 1H), 8.09 (dd, J= 9.0,2.3 Hz, 1H), 9.97 (d, J= 8.2 Hz, 2H), 7.51 (d, J= 8.2 Hz, 2H), 7.46 (d, J= 8.8 Hz, 1H), 7.30 (d, J= 7.0 Hz, 1H), 7.17 (t, J= 7.8 Hz, 1H), 7.10 (d, J= 7.8 Hz, 1H), 7.03 (t, J= 7.2 Hz, 1H), 4.75 (d, J= 5.5 Hz, 2H). m/z: 420.5 (MH^+).

Example 79

4-[(6-Amino-benzothiazol-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide (144)

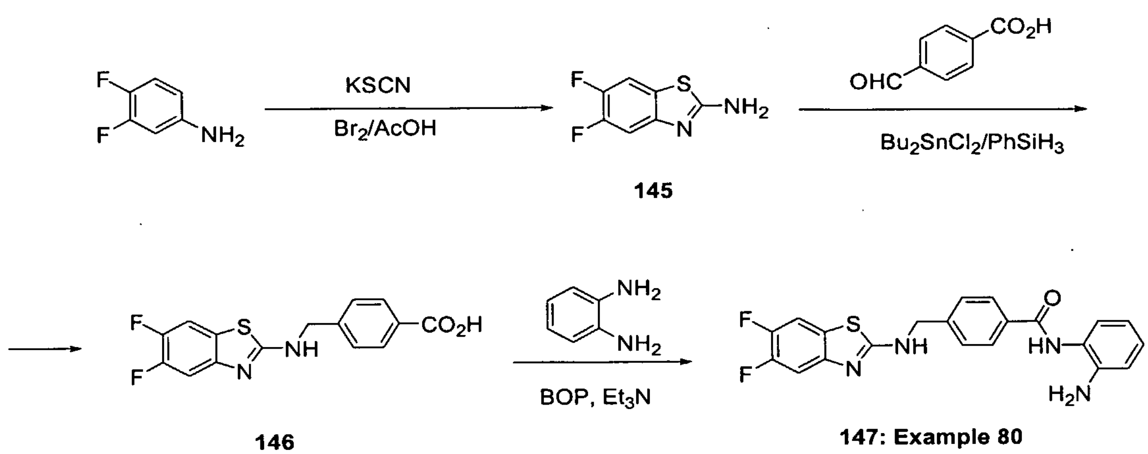
[0523] Step 1: (2-{4-[(6-Amino-benzothiazol-2-ylamino)-methyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (143):

[0524] To a suspension of compound **141** (200 mg, 0.385 mmol) in a mixture of THF/MeOH/H_2O (10mL/10mL/10mL) were successively added tin(II) chloride dihydrate (1.35g, 8.46 mmol) and ammonium acetate (1.09 g, 14.12 mmol). The mixture was refluxed for 2 days, the tin salts were filtered off and the filtrate was concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O (brine was added to break the emulsion). Organic phase was successively washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound **143** (145 mg, 77% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 12.89 (bs, 1H), 10.79 (s, 1H), 8.12 (d, J= 2.0 Hz, 1H), 8.05 (d, J= 8.8 Hz, 2H), 7.90-7.68 (m, 3H), 7.62 (d, J= 8.4 Hz, 2H), 7.48 (bs, 1H), 7.21 (dd, J= 4.9, 3.7 Hz, 1H), 4.65 (s, 2H). m/z: 490.5 (MH^+).

[0525] Step 2: 4-[(6-Amino-benzothiazol-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide (144)

[0526] The title compound **144** was obtained following the same procedures as for the Boc-cleavage described in scheme 28, step 5 (example 68) using compound **143** as starting material. (58% yield). ^{1}H NMR: (DMSO-d_6): 9.58 (s, 1H), 8.09 (t, J= 5.9 Hz, 1H), 7.91 (d, J= 8.0 Hz, 2H), 7.45 (d, J= 8.4 Hz, 2H), 7.13 (d, J= 7.0 Hz, 1H), 7.05 (d, J= 8.6 Hz, 1H), 6.94 (t, J= 6.8 Hz, 1H), 6.81 (d, J= 2.2 Hz, 1H), 6.75 (dd, J= 6.7,1.2 Hz, 1H), 6.57 (t, J= 6.5 Hz, 1H), 6.48 (dd, J= 8.4,2.2 Hz, 1H), 5.19 (s, 2H), 4.81 (s, 2H), 4.58 (d, J= 5.9 Hz, 2H). m/z: 390.5 (MH$^+$).

Scheme 34



Example 80

N-(2-Amino-phenyl)-4-[(5,6-difluoro-benzothiazol-2-ylamino)-methyl]-benzamide (147)

[0527] Step 1: 5,6-Difluoro-benzothiazol-2-ylamine (145):

[0528] The title compound **145** was obtained following the procedure described in *J.Het.Chem*, **1971**, *8* (309-310) starting from 4,5-difluoroaniline (95% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 7.78 (dd, J= 10.6, 8.6 Hz, 1H), 7.61 (s, 2H), 7.32 (dd, J= 11.9, 7.2 Hz, 1H). m/z: 337.5 (M+Na$^+$)

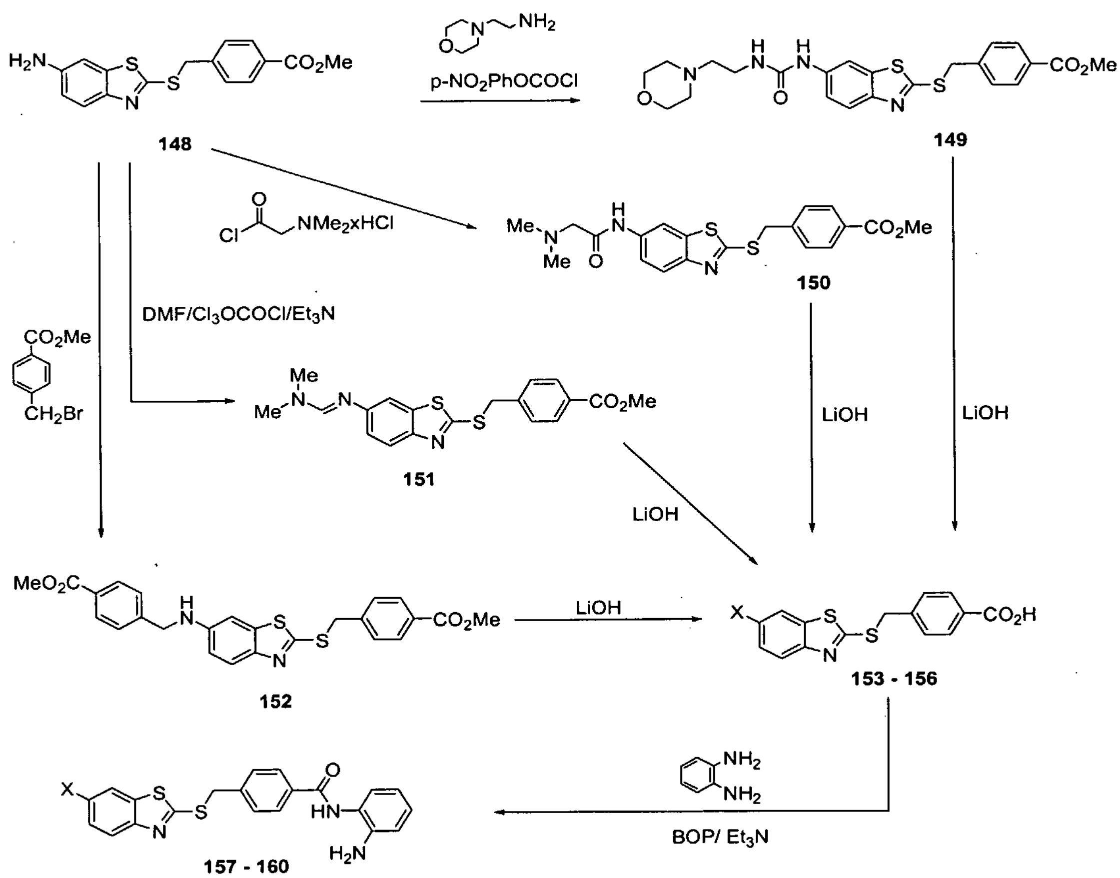
[0529] Step 2: 4-[(5,6-Difluoro-benzothiazol-2-ylamino)-methyl]-benzoic acid (146):

[0530] The title compound **146** was obtained starting from the compound **145** following the same procedure as for the reductive amination described in scheme 3, step 2 (example 12) (63% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 8.72 (t, J =5.9 Hz, 1H), 7.89 (d, J= 8.4 Hz, 2H), 7.82 (dd, J= 10.4, 8.0 Hz, 1H), 7.44 (d, J= 8.4 Hz, 2H), 7.40 (dd, J= 11.9, 7.4 Hz, 1H), 4.65 (d, J= 5.7 Hz, 2H). m/z: 315.2 (MH$^+$).

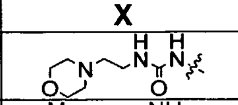
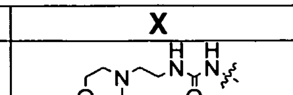
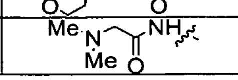
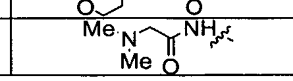
[0531] Step 3: N-(2-Amino-phenyl)-4-[(5,6-difluoro-benzothiazol-2-ylamino)-methyl]-benzamide (147):

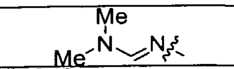
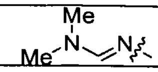
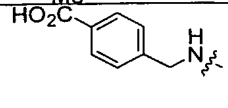
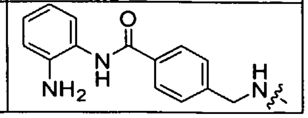
[0532] The title compound **147** was obtained starting from the compound **146** following the same procedure as for the BOP coupling reaction described in scheme 1, step 5 (example 1) (32% yield). ^{1}H NMR: (DMSO-d$_6$): 9.59 (s, 1H), 8.73 (t, J= 5.9 Hz, 1H), 7.93 (d, J= 8.2 Hz, 2H), 7.83 (dd, J= 10.4, 8.0 Hz, 1H), 7.45 (d, J= 8.2 Hz, 2H), 7.40 (dd, J= 11.9, 7.2 Hz, 1H), 7.13 (d, J= 7.8 Hz, 1H), 6.94 (td, J= 7.8, 1.4 Hz, 1H), 6.75 (dd, J= 7.8, 1.4 Hz, 1H), 6.57 (td, J= 7.6, 1.2 Hz, 1H), 4.87 (s, 2H), 4.65 (d, J= 5.9 Hz, 2H). m/z: 411.4 (MH$^+$).

Scheme 35



157: Example 81
158: Example 82
159: Example 83
160: Example 84

Compound	X		Compound	Example	X
153			157	81	
154			158	82	

Compound	X		Compound	Example	X
155			159	83	
156			160	84	

Example 81

N-(2-Amino-phenyl)-4-{6-[3-(2-morpholin-4-yl-ethyl)-ureido]-benzothiazol-2-ylsulfanylmethyl}-benzamide (157)

[0533] Step 1: 4-{6-[3-(2-Morpholin-4-yl-ethyl)-ureido]-benzothiazol-2-ylsulfanylmethyl}-benzoic acid methyl ester (149):

[0534] The title compound **149** was obtained following the same procedure as for the carbamate formation described in scheme 32, step 1 (example 75), but substituting compound **129** for compound **148** (described in the Patent Application WO 03/024448) (70% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.28 (bs, 1H), 8.18 (d, J= 2.3 Hz, 1H), 7.90 (d, J= 8.2 Hz, 2H), 7.77 (d, J= 8.6 Hz, 1H), 7.61 (d, J= 8.2 Hz, 2H), 7.42 (dd, J= 8.8, 2.2 Hz, 1H), 4.68 (s, 2H), 3.82 (s, 3H), 3.59-3.58 (m, 4H), 3.33-3.32 (m, 2H), 3.21 (q, J=6.1 Hz, 2H), 2.38-2.37 (m, 4H). m/z: 487.4 (MH^+).

[0535] Step 2: 4-{6-[3-(2-Morpholin-4-yl-ethyl)-ureido]-benzothiazol-2-ylsulfanylmethyl}-benzoic acid methyl ester (153):

[0536] The title compound **153** was obtained following the same procedure as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **149** as starting material (50% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.75 (bs, 1H), 8.22 (d, J= 2.2 Hz, 1H), 7.90 (d, J= 8.4 Hz, 2H), 7.76 (d, J= 8.8 Hz, 1H), 7.61 (d, J= 8.4 Hz, 2H), 7.55 (d, J= 6.3 Hz, 1H), 7.49 (dd, J= 8.8, 2.2 Hz, 1H), 4.68 (s, 2H), 3.58 (t, J= 4.3 Hz, 4H), 3.34-3.32 (m, 2H), 3.21 (q, J= 5.9 Hz, 2H), 2.38 (t, J= 6.3 Hz, 4H). m/z: 473.4 (MH^+).

[0537] Step 3: N-(2-Amino-phenyl)-4-{6-[3-(2-morpholin-4-yl-ethyl)-ureido]-benzothiazol-2-ylsulfanylmethyl}-benzamide (157)

[0538] The title compound **157** was obtained following the same procedures as the BOP coupling described in scheme 1, step 5 (example 1) using compound **153** as starting material (26% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.59 (s, 1H), 8.84 (s, 1H), 8.13 (d, J= 2.2 Hz, 1H), 7.90 (d, J= 8.2 Hz, 2H), 7.71 (d, J= 8.6 Hz, 1H), 7.58 (d, J= 8.2 Hz, 2H), 7.30 (dd, J= 8.8, 2.2 Hz 1H), 7.12 (d, J= 7.0 Hz, 1H), 6.94 (t, J= 7.0 Hz, 1H), 6.74 (dd, J=8.1, 1.5 Hz, 1H), 6.56 (t,

J= 7.4 Hz, 1H), 6.14 (t, J= 4.9 Hz, 1H), 4.88 (bs, 2H), 4.66 (s, 2H) 3.58 (t, J= 4.5 Hz, 4H), 3.31-3.30 (m, 2H), 3.21 (q, J= 5.7 Hz, 2H), 2.38 (t, J= 6.3 Hz, 4H). m/z: 563.5 (MH^+).

Example 82

N-(2-Amino-phenyl)-4-[6-(2-dimethylamino-acetylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (158)

[0539] Step 1: 4-[6-(2-Dimethylamino-acetylamino)-benzothiazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (150):

[0540] $NaHCO_3$ (356mg, 4.24 mmol) was added to a suspension of compound **148** (described in the Patent Application WO 03/024448) (701 mg, 2.12 mmol) and $Me_2NCH_2COCl{\cdot}HCl$ (670mg, 4.24 mmol) in CH_3CN followed by addition of Et_3N (295µl, 2.12 mmol). The mixture was stirred at room temperature 24h, concentrated *in vacuo* and the residue was partitioned between DCM and H_2O. The aqueous layer was collected, neutralized with $NaHCO_3$ and extracted with fresh DCM, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel affording the title compound **150** (485mg, 55% yield). ^1H NMR: (DMSO-d_6) δ(ppm): 9.95 (s, 1H), 8.41 (d, J= 2.0 Hz, 1H), 7.91 (d, J= 8.2 Hz, 2H), 7.79 (d, J= 8.8 Hz, 1H), 7.63 (d, J= 8.2 Hz, 2H), 7.63 (dd, J= 8.8, 2.1 Hz, 1H), 4.71 (s, 2H), 3.84 (s, 3H), 3.11 (s, 2H), 2.30 (s, 6H). m/z: 416.4 (MH^+).

[0541] Step 2: 4-[6-(2-Dimethylamino-acetylamino)-benzothiazol-2-ylsulfanylmethyl]-benzoic acid (154):

[0542] The title compound **154** was obtained following same procedure as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **150** as starting material (78% yield). ^1H NMR: (DMSO-d_6) δ(ppm): 9.95 (s, 1H), 8.41 (d, J= 2.0 Hz, 1H), 7.86 (d, J= 8.2 Hz, 2H), 7.79 (d, J= 8.8 Hz, 1H), 7.63 (dd, J= 9.0, 2.0 Hz, 1H), 7.55 (d, J= 8.2 Hz, 2H), 4.68 (s, 2H), 3.11 (s, 2H), 2.30 (s, 6H). m/z: 402.4 (MH^+).

[0543] Step 3: N-(2-Amino-phenyl)-4-[6-(2-dimethylamino-acetylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (158)

[0544] Title compound **158** was obtained following the same procedures as the BOP coupling described in scheme 1, step 5 (example 1) using compound **154** as starting material (28% yield). ^1H NMR: (DMSO-d_6) δ (ppm): 9.93 (s, 1H), 9.59 (s, 1H), 8.39 (d, J= 2.0 Hz, 1H), 7.90 (d, J= 8.0 Hz, 2H), 7.79 (d, J= 9.0 Hz, 1H), 7.62 (dd, J= 8.8, 2.2 Hz, 1H), 7.60 (d, J= 8.2 Hz, 2H), 7.12 (d, J= 7.6 Hz, 1H), 6.94 (t, J= 8.0 Hz, 1H), 6.74 (dd, J= 8.0, 1.6 Hz, 1H), 6.56 (t, J= 7.5 Hz, 1H), 4.88 (s, 2H), 4.69 (s, 2H), 3.09 (s, 2H), 2.28 (s, 6H). HRMS: m/z: 491.1455±0.0014 (M^+).

Example 83

N-(2-Amino-phenyl)-4-[6-(dimethylamino-methyleneamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (159)

[0545] Step 1: 4-[6-(Dimethylamino-methyleneamino)-benzothiazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (151):

[0546] To a pre-cooled (-78°C) solution of trichloromethylchloroformate (74μL, 608 mmol) in THF (2 mL) under N_2 atmosphere was added *via canula* a solution of compound **148** (described in the Patent Application WO 03/024448) (201mg, 608 mmol) in a mixture of THF and DMF (3.5 mL, 0.5 mL respectively) followed by addition of Et_3N (169 μL, 1.22 mmol). The solution was stirred at -78°C for 1 h and at 0°C for 2 h and allowed to warm to rt overnight. The solvents were removed *in vacuo*, and the residue was partitioned between H_2O and a mixture of DCM /MeOH (9:1), dried over $MgSO_4$ and concentrated *in vacuo*, affording the title compound **151** (136 mg, 58% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 7.92 (d, J= 8.4 Hz, 2H), 7.81 (s, 1H), 7.69 (d, J= 8.6 Hz, 1H), 7.62 (d, J= 8.2 Hz, 2H), 7.46 (d, J= 2.2 Hz, 1H), 7.04 (dd, J= 8.6, 2.2 Hz, 1H), 4.68 (s, 2H), 3.84 (s, 3H), 3.04 (bs, 3H), 2.95 (bs, 3H). m/z: 386.4 (MH^+).

[0547] Step 2: 4-[6-(Dimethylamino-methyleneamino)-benzothiazol-2-ylsulfanylmethyl]-benzoic acid (155):

[0548] The title compound **155** was obtained following same procedure as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **151** as starting material (45% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 7.89 (d, J= 8.2 Hz, 2H), 7.80 (s, 1H), 7.69 (d, J= 8.6 Hz, 1H), 7.59 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 2.2 Hz, 1H), 7.04 (dd, J= 8.6, 2.2 Hz, 1H), 4.67 (s, 2H), 3.03 (bs, 3H), 2.94 (bs, 3H). m/z: 372.3 (MH^+).

[0549] Step 3: N-(2-Amino-phenyl)-4-[6-(dimethylamino-methyleneamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (159)

[0550] The title compound **159** was obtained following the same procedures as for the BOP coupling described in scheme 1, step 5 (example 1) using compound **155** as starting material. (25% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.60 (s, 1H), 7.91 (d, J= 8.2 Hz, 2H), 7.79 (s, 1H), 7.69 (d, J= 8.6 Hz, 1H), 7.60 (d, J= 8.2 Hz, 2H), 7.44 (d, J= 2.2 Hz, 1H), 7.13 (d, J= 8.0 Hz, 1H), 7.03 (dd, J= 8.6, 2.3 Hz, 1H), 6.95 (t, J= 7.0 Hz, 1H), 6.75 (d, J= 9.2 Hz, 1H), 6.57 (t, J= 7.4 Hz, 1H), 4.89 (s, 2H), 4.67 (s, 2H), 3.02 (s, 3H), 2.93 (s, 3H). m/z: 462.5 (MH^+).

Example 84

***N*-(2-Amino-phenyl)-4-{6-[*N*-(2-Amino-phenyl)-4-benzylamide]-benzothiazol-2-ylsulfanylmethyl}-benzamide (160)**

[0551] Step 1: N-(4-methylbenzoic acid methyl ester)-benzothiazol-2-ylsulfanylmethyl}-benzoic acid methyl ester (152):

[0552] To a solution of compound **148** (9.52g, 28.8 mmol) in DMF (30 mL) was added DCM (130 mL) and methyl-(4-bromomethyl)benzoate (6.60g, 28.8 mmol) was added and the mixture was stirred at rt for 16h. The solvents were concentrated *in vacuo* and the resulting solid was partitioned between EtOAc and H_2O. The organic layer was washed with HCl 1N, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography using EtOAc/Hex (45:55) followed by Biotage pre-packed silica gel column using MeOH/DCM (2:98) and crystallization in a mixture of $CHCl_3$ and Et_2O affording the title compound **152** (2.66g, 19% yield). ^1H NMR: (DMSO-d_6) δ(ppm): 7.89 (d, J= 8.0 Hz, 2H), 7.87 (d, J= 7.8 Hz, 2H), 7.55 (d, J= 8.4 Hz, 2H), 7.54 (d, J= 8.8 Hz, 1H), 7.47 (d, J= 8.4 Hz, 2H), 6.93 (d, J= 2.3 Hz, 1H), 6.77 (dd, J= 8.8, 2.5 Hz, 1H), 6.70 (t, J= 6.1 Hz, 1H), 4.58 (s, 2H), 4.38 (d, J= 6.3 Hz, 2H), 3.81 (s, 3H), 3.81 (s, 3H). m/z: 479.4 (MH^+).

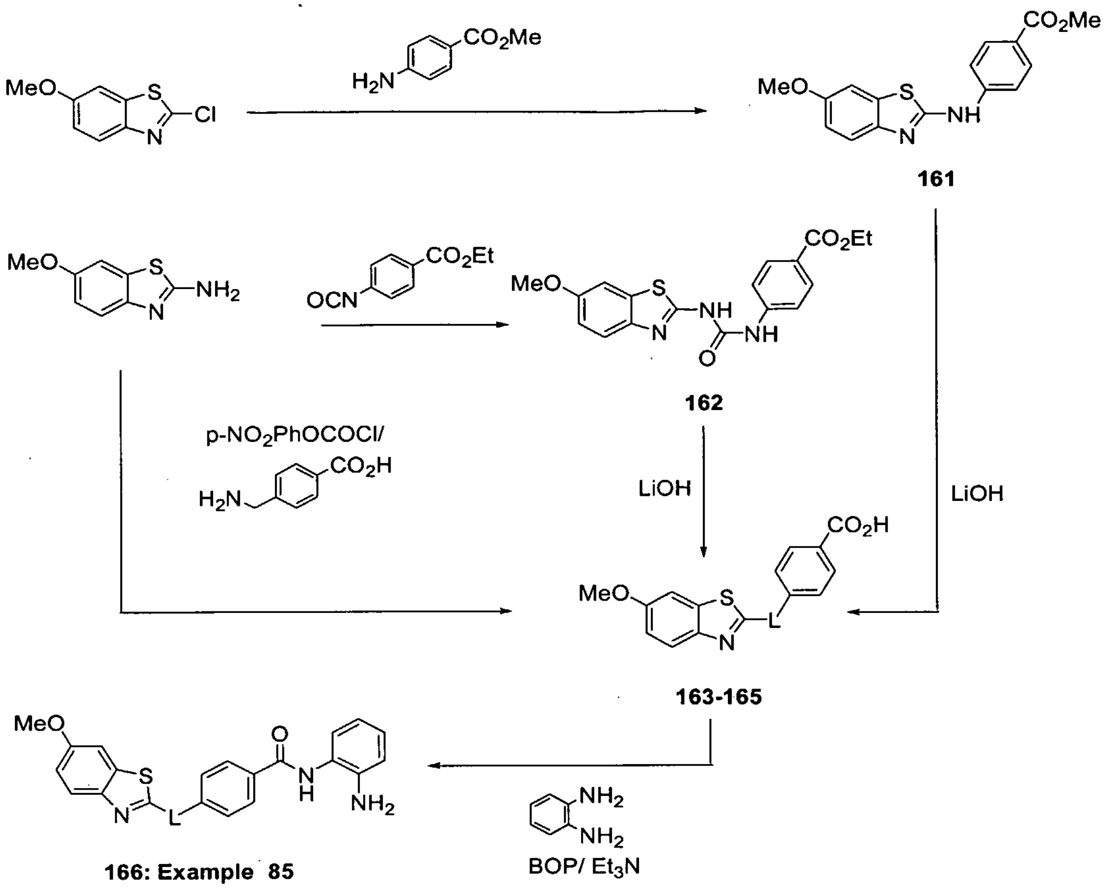
[0553] Step 2: N-(4-methylbenzoic acid)-benzothiazol-2-ylsulfanylmethyl}-benzoic acid (156):

[0554] The title compound **156** was obtained following same procedure as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **152** as starting material and doubling the amount of lithium hydroxide (37% yield). m/z: 451.4 (MH^+).

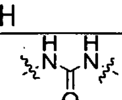
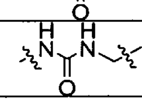
[0555] Step 3: N-(2-Amino-phenyl)-4-{6-[N-(2-Amino-phenyl)-4-benzamide]- benzothiazol-2-ylsulfanylmethyl}-benzamide (160)

[0556] The title compound **160** was obtained following the same procedures as for the BOP coupling described in scheme 1, step 5 (example 1) using compound **156** as starting material and doubling the amount of all reagents (5% yield). ^1H NMR: (Acetone-d_6) d(ppm): 7.98 (d, J= 8.0 Hz, 2H), 7.96 (d, J= 8.2 Hz, 2H), 7.63 (d, J= 9.0 Hz, 1H), 7.62 (d, J= 7.4 Hz, 2H), 7.55 (d, J= 8.0 Hz, 2H), 7.28 (d, J= 8.2 Hz, 2H), 7.04 (d, J= 2.5 Hz, 1H), 6.99 (t, J= 7.4 Hz, 2H), 6.91 (dd, J= 8.8, 2.3 Hz, 1H), 6.85 (d, J= 7.4 Hz, 2H), 6.66 (t, J= 7.4 Hz, 2H), 4.65 (s, 2H), 4.54 (s, 2H). m/z: 631.5 (MH^+).

Scheme 36



166: Example 85
167: Example 86
168: Example 87

Compounds	Example	L
163, 166	85	NH
164, 167	86	
165, 168	87	

Example 85

N-(2-Amino-phenyl)-4-(6-methoxy-benzothiazol-2-ylamino)-benzamide (166)

[0557] Step 1: 4-(6-Methoxy-benzothiazol-2-ylamino)-benzoic acid methyl ester (161):

[0558] To a solution of 2-chloro-6-methoxybenzothiazole (1.00g, 5.03 mmol) in DMF (10 mL) was added methyl 4-aminobenzoate (760mg, 5.03 mmol) followed by addition of powdered K_2CO_3 (1.81g, 15.09 mmol). The mixture was stirred at 90°C for 16 h and at 120°C for 24 h and then at 140°C for 3 days. It was allowed to cool down to rt and NaH (60% in mineral oil, 201mg, 5.03 mmol) was added. The mixture was stirred at rt for 16 h and quenched with H_2O. The solvent was removed *in vacuo* at 80°C and the residue was partitioned between H_2O and EtOAc.

The organic layer was washed with HCl 1N, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography using EtOAc/Hex and increasing polarity from 20:80 to 50:50 throughout elution, affording the title compound **161** (150mg, 9% yield). m/z: 315.2 (MH^+)

[0559] Step 2: 4-(6-Methoxy-benzothiazol-2-ylamino)-benzoic acid (163):

[0560] The title compound **163** was obtained following same procedure as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **161** as starting material (66% yield). m/z: 301.2 (MH^+).

[0561] Step 3: N-(2-Amino-phenyl)-4-(6-methoxy-benzothiazol-2-ylamino)-benzamide (166)

[0562] The title compound **166** was obtained following the same procedures as for the BOP coupling described in scheme 1, step 5 (example 1) using compound **163** as starting material. (53% yield). ^1H NMR: (DMSO-d_6) δ(ppm): 10.62 (s, 1H), 9.53 (s, 1H), 7.98 (d, J=8.8 Hz, 2H), 7.84 (d, J=9.2 Hz, 2H), 7.57 (d, J=8.8 Hz, 1H), 7.47 (d, J=2.0 Hz, 1H), 6.59 (t, J=7.2 Hz, 1H), 4.89 (s, 2H), 3.78 (s, 3H). m/z: 391.4 (MH^+).

Example 86

N-(2-Amino-phenyl)-4-[3-(6-methoxy-benzothiazol-2-yl)-ureido]-benzamide (167)

[0563] Step 1: 4-[3-(6-Methoxy-benzothiazol-2-yl)-ureido]-benzoic acid ethyl ester (162):

[0564] The title compound **162** was obtained following the procedure described in *J.Med.Chem.*, **1979**, *22* (1), 28-32, starting from 2-amino-6-methoxybenzothiazole (93% yield). ^1H NMR: (DMSO-d_6) δ(ppm): 9.63 (bs, 1H), 7.91 (d, J= 8.4 Hz, 2H), 7.65 (d, J= 8.0 Hz, 2H), 7.55-7.51 (m, 2H), 6.98 (d, J= 8.8 Hz, 1H), 4.28 (q, J= 6.8 Hz, 2H), 3.79 (s, 3H), 1.32 (t, J= 7.2 Hz, 3H). m/z: 372.3 (MH^+).

[0565] Step 2: 4-[3-(6-Methoxy-benzothiazol-2-yl)-ureido]-benzoic acid (164):

[0566] The title compound **164** was obtained following same procedure as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **162** as starting material (99% yield). ^1H NMR: (DMSO-d_6) δ (ppm): 7.94 (d, J= 8.4 Hz, 2H), 7.70 (d, J= 8.0 Hz, 2H), 7.57 (d, J= 8.4 Hz, 1H), 7.49 (d, J= 2.4 Hz, 1H), 6.96 (dd, J= 8.8, 2.4 Hz, 1H), 3.80 (s, 3H). m/z: 344.3 (MH^+).

[0567] Step 3: N-(2-Amino-phenyl)-4-[3-(6-methoxy-benzothiazol-2-yl)-ureido]-benzamide (167)

[0568] The title compound **167** was obtained following the same procedures as the BOP coupling described in scheme 1, step 5 (example 1) using compound **164** as starting material. (50% yield). ^1H NMR: (DMSO-d_6) δ(ppm): 9.58 (s, H), 9.54 (bs, 1H), 7.96 (d, J= 8.4 Hz, 2H), 7.93 (s, 1H), 7.63 (d, J= 8.8 Hz, 2H), 7.54 (d, J= 9.2 Hz, 1H), 7.52 (d, J=2.0 Hz, 1H), 7.14 (d, J= 7.6

Hz, 1H), 6.98 (dd, J= 8.0,1.6 Hz, 1H), 6.94 (d, J= 8.0 Hz, 1H), 6.77 (d, J= 8.0 Hz, 1H), 6.59 (t, J= 7.2 Hz, 1H), 4.89 (bs, 2H), 3.80 (s, 3H). m/z: 434.4 (MH^+).

Example 87

N-(2-Amino-phenyl)-4-[3-(6-methoxy-benzothiazol-2-yl)-ureidomethyl]-benzamide (168)

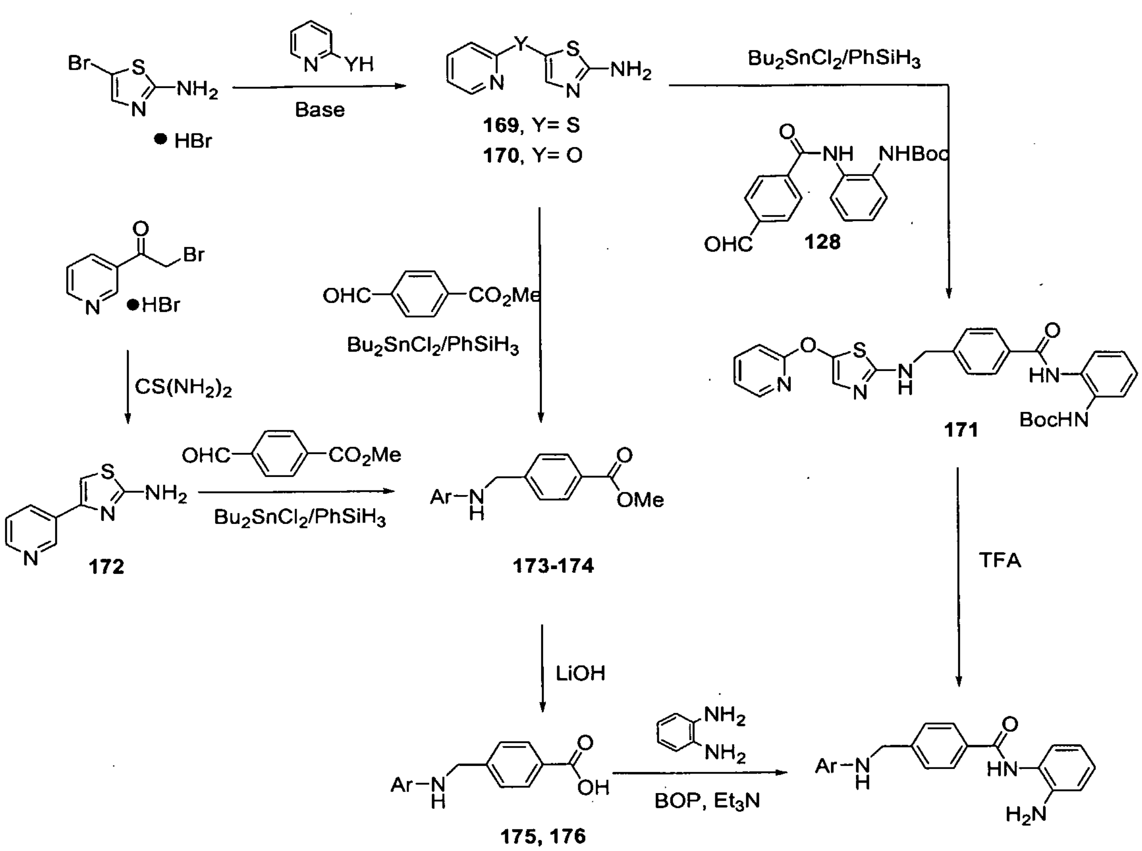
[0569] Step 1: 4-[3-(6-Methoxy-benzothiazol-2-yl)-ureidomethyl]-benzoic acid (165):

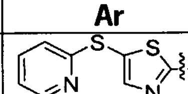
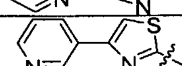
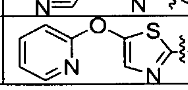
[0570] The title compound **165** was obtained following the same procedure as for the carbamate formation described in scheme 32, step 1 (example 75) substituting compound **129** for 2-amino-6-methoxybenzothiazole and using 4-aminomethylbenzoic acid instead of 4-(2-aminoethyl)-morpholine (28% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 7.92 (t, J= 8.0 Hz, 2H), 7.51 (d, J= 8.5 Hz, 1H), 7.47 (s, 1H), 7.42 (d, J= 8.5 Hz, 1H), 6.95 (d, J= 7.0 Hz, 1H), 4.45 (s, 2H), 3.77 (s, 3H). m/z: 358.3 (MH^+).

[0571] Step 2: N-(2-Amino-phenyl)-4-[3-(6-methoxy-benzothiazol-2-yl)-ureidomethyl]-benzamide (168)

[0572] The title compound **168** was obtained following the same procedures as the BOP coupling described in scheme 1, step 5 (example 1) using compound **165** as starting material. (1.5% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 10.75 (bs, 14H), 9.63 (s, 1H), 7.97-7.91 (m, 2H), 7.53-7.43 (m, 3H), 7.33 (s, 1H), 7.16 (s, 1H), 6.96-6.95 (m, 2H), 6.78 (d, J=8.0 Hz, 1H), 6.60-6.58 (m, 1H), 4.88 (bs, 2H), 4.45 (s, 2H), 3.78 (s, 3H).

Scheme 37



Compounds	Ar
173, 175, 177	
174, 176, 179	
178	

Example 88

N-(2-Amino-phenyl)-4-{[5-(pyridin-2-ylsulfanyl)-thiazol-2-ylamino]-methyl}-benzamide (177)

[0573] Step 1: 5-(Pyridin-2-ylsulfanyl)-thiazol-2-ylamine (169):

[0574] To a solution of 2-amino-5-bromothiazole hydrobromide (1.00g, 3.85 mmol) in DMF (8 mL) was added 2-mercaptopyridine (428mg, 3.85 mmol) followed by addition of powdered K_2CO_3 (1.81g, 15.09 mmol). The mixture was stirred at 80°C for 1 h and at rt for 16h. The solvent was removed *in vacuo* at 80°C and the compound was partitioned between H_2O and

EtOAc. The aqueous layer was extracted with EtOAc and the organic phase was extracted with HCl 1N. The acidic extract was neutralized with saturated $NaHCO_3$ and the precipitate was extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound **169** (589mg, 73% yield). ^{1}H NMR: (Acetone-d_6) δ(ppm): 8.36 (s, 1H), 7.66 (s, 1H), 7.20 (s, 1H), 7.12-7.05 (m, 2H), 6.84 (s, 2H). m/z: 210.1 (MH^+).

[0575] Step 2: 4-{[5-(Pyridin-2-ylsulfanyl)-thiazol-2-ylamino]-methyl}-benzoic acid methyl ester (173):

[0576] The title compound **173** was obtained starting from the compound **169** following the same procedures as for the reductive amination described in scheme 3, step 2 (example 12) (50% yield). ^{1}H NMR: (Acetone-d_6) δ(ppm): 8.37 (d, J= 4.0 Hz, 1H), 7.99 (d, J= 8.5 Hz, 2H), 7.83 (bs, 1H), 7.67 (td, J= 8.0, 1.5 Hz, 1H), 7.56 (d, J= 7.5 Hz, 2H), 7.28 (s, 1H), 7.13 (dd, J= 6.5, 5.0 Hz, 1H), 7.07 (d, J= 8.0 Hz, 1H), 4.72 (bs, 2H), 3.88 (s, 3H). m/z: 358.1 (MH^+).

[0577] Step 3: 4-{[5-(Pyridin-2-ylsulfanyl)-thiazol-2-ylamino]-methyl}-benzoic acid (175):

[0578] The title compound **175** was obtained following the same procedures as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **173** as starting material. (81% yield). ^{1}H NMR: (acetone-d_6) δ (ppm): 8.37 (d, J= 4.0Hz, 1H), 7.99 (d, J= 8.5 Hz, 2H), 7.83 (bs, 1H), 7.67 (td, J= 8.0, 1.5 Hz, 1H), 7.56 (d, J= 7.5 Hz, 2H), 7.28 (s, 1H), 7.13 (dd, J= 6.5, 5.0 Hz, 1H), 7.07 (d, J= 8.0 Hz, 1H), 4.72 (bs, 2H), 3.88 (s, 3H). m/z: 344.0 (MH^+).

[0579] Step 4: N-(2-Amino-phenyl)-4-{[5-(pyridin-2-ylsulfanyl)-thiazol-2-ylamino]-methyl}-benzamide (177)

[0580] The title compound **177** was obtained following the same procedures as for the BOP coupling described in scheme 1, step 5 (example 1) using compound **175** as starting material. (53% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.63 (s, 1H), 8.74 (t, J= 5.9 Hz, 1H), 8.40 (d, J= 3.7 Hz, 1H), 7.96 (d, J= 8.4 Hz, 2H), 7.72 (td, J= 7.6, 2.0 Hz, 1H), 7.48 (d, J= 7.8 Hz, 2H), 7.34 (s, 1H), 7.19-7.15 (m, 2H), 7.05 (d, J= 8.2 Hz, 1H), 6.97 (t, J=8.0 Hz, 1H), 6.78 (d, J= 7.8 Hz, 1H), 6.60 (t, J= 7.8 Hz, 1H), 4.91 (s, 2H), 4.59 (d, J= 6.1 Hz, 2H). mz: 434.4 (MH^+).

Example 89

N-(2-Amino-phenyl)-4-{[5-(pyridin-2-yloxy)-thiazol-2-ylamino]-methyl}-benzamide (178)

[0581] Step 1: 5-(Pyridin-3-yloxy)-thiazol-2-ylamine (170):

[0582] To a suspension of (NaH 60% in mineral oil, 169mg, 4.23mmol) in DME (10 mL) was added 2-hydroxypyridine (366mg, 3.85 mmol). [Hydrogen evolution was observed]. Then, powdered K_2CO_3 (2.31g, 19.2 mmol) was added followed by portion-wise addition of 2-amino-5-bromothiazole hydrobromide (1.00g, 3.85 mmol). The mixture was refluxed with stirring for 16 h

and allowed to cool down to room temperature, quenched with water and partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc and organic phase was extracted with HCl 1N. The acidic extract was neutralized with saturated $NaHCO_3$ and the precipitate was extracted first with EtOAc and then with a mixture of MeOH/$CHCl_3$ (20:85). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was crystallized by addition of a mixture of MeOH/$CHCl_3$ (5:95) affording the title compound **170** (21mg, 3%). ^{1}H NMR: (CD_3OD) δ(ppm): 9.05 (dd, J= 7.2, 2.0 Hz, 1H), 8.70 (ddd, J= 9.2, 6.7, 2.2 Hz, 1H), 8.44 (s, 1H), 7.73 (d, J= 8.8 Hz, 1H), 7.59 (bs, 2H), 7.58 (td, J= 6.8, 1.4 Hz, 1H). m/z: 194.2 (MH^+).

[0583] Step 2: [2-(4-{[5-(Pyridin-3-yloxy)-thiazol-2-ylamino]-methyl}-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (173):

[0584] The title compound **173** was obtained following same procedure as for the reductive amination described in scheme 3, step 2 (example 12) reacting compound **170** with compound **128** (described in the Patent Application WO 03/024448) (46% yield). ^{1}H NMR: (acetone-d_6) δ (ppm): 9.66 (s, 1H), 8.30 (s, 1H), 7.97 (d, J= 8.2 Hz, 2H), 7.79 (ddd, J= 7.0, 2.0, 0.6 Hz, 1H), 7.68 (dd, J= 7.6, 1.6 Hz, 1H), 7.60 (dd, J= 7.8, 1.8 Hz, 1H), 7.55 (d, J= 8.2 Hz, 2H), 7.45 (ddd, J= 9.4, 6.7, 2.0 Hz, 1H), 7.27 (s, 1H), 7.21 (td, J= 7.4, 1.8 Hz, 1H), 7.16 (dt, J= 7.4, 1.8 Hz, 1H), 6.50 (d, J= 9.2 Hz, 1H), 6.33 (td, J= 6.7, 1.4 Hz, 1H), 4.67 (s, 2H), 1.99 (s, 9H).m/z: 518.5 (MH^+).

[0585] Step 3: N-(2-Amino-phenyl)-4-{[5-(pyridin-2-yloxy)-thiazol-2-ylamino]-methyl}-benzamide (178)

[0586] The title compound **178** was obtained following the same procedures as for the Boc cleavage described in scheme 28, step 5 (example 68) using compound **171** as starting material. (82% yield). ^{1}H NMR: (acetone-d_6) δ (ppm): 8.00 (d, J= 8.4 Hz, 2H), 7.82 (dd, J= 6.3, 1.4 Hz, 1H), 7.56 (d, J= 8.2 Hz, 2H), 7.46 (ddd, J= 13.7, 6.7, 2.2 Hz, 1H), 7.30 (d, J=6.7 Hz, 1H), 7.28 (s, 1H), 6.99 (td, J= 13.7, 7.2 Hz, 1H), 6.87 (dd, J= 6.7, 1.2 Hz, 1H), 6.67 (t, J= 7.2 Hz, 1H), 6.49 (d, J= 8.8 Hz, 1H), 6.34 (td, J= 6.7, 5.3 Hz, 1H), 4.69 (s, 2H). m/z: 434.4 (MH^+).

Example 90

N-(2-Amino-phenyl)-4-[(4-pyridin-3-yl-thiazol-2-ylamino)-methyl]-benzamide (179)

[0587] Step 1: 4-Pyridin-3-yl-thiazol-2-ylamine (172):

[0588] The title compound **172** was obtained following the procedure described in *J. Heterocycl. Chem.*, **1970**, *7*, (1137-1141). (94% yield). ^{1}H NMR: (CD_3OD) δ(ppm): 8.94 (dd, J= 2.3, 0.8 Hz, 1H), 8.41 (dd, J= 4.7, 1.6 Hz, 1H), 8.18 (dt, J= 8.6, 1.6 Hz, 1H), 7.43 (ddd, J= 9.0, 3.9, 0.8 Hz, 1H), 7.03 (s, 1H). m/z: 178.1 (MH^+).

[0589] Step 2: 4-[(4-Pyridin-3-yl-thiazol-2-ylamino)-methyl]-benzoic acid methyl ester (174):

[0590] The title compound **174** was obtained following the same procedures as for the reductive amination described in scheme 3, step 2 (example 12) using compound **172** as starting material (33% yield). ^{1}H NMR: (Acetone-d_6) δ(ppm): 9.07 (dd, J= 2.3, 0.8 Hz, 1H), 8.45 (dd, J= 4.7, 1.6 Hz, 1H), 8.16 (dt, J= 8.6, 1.6 Hz, 1H), 7.98 (d, J= 8.6 Hz, 2H), 7.60 (d, J= 8.6 Hz, 2H), 7.52-7.49 (m, 1H), 7.34 (ddd, J= 7.8, 4.7, 0.8, 1H), 7.14 (s, 1H), 4.76 (s, 2H), 3.87 (s, 3H). m/z: 326.3 (MH^+).

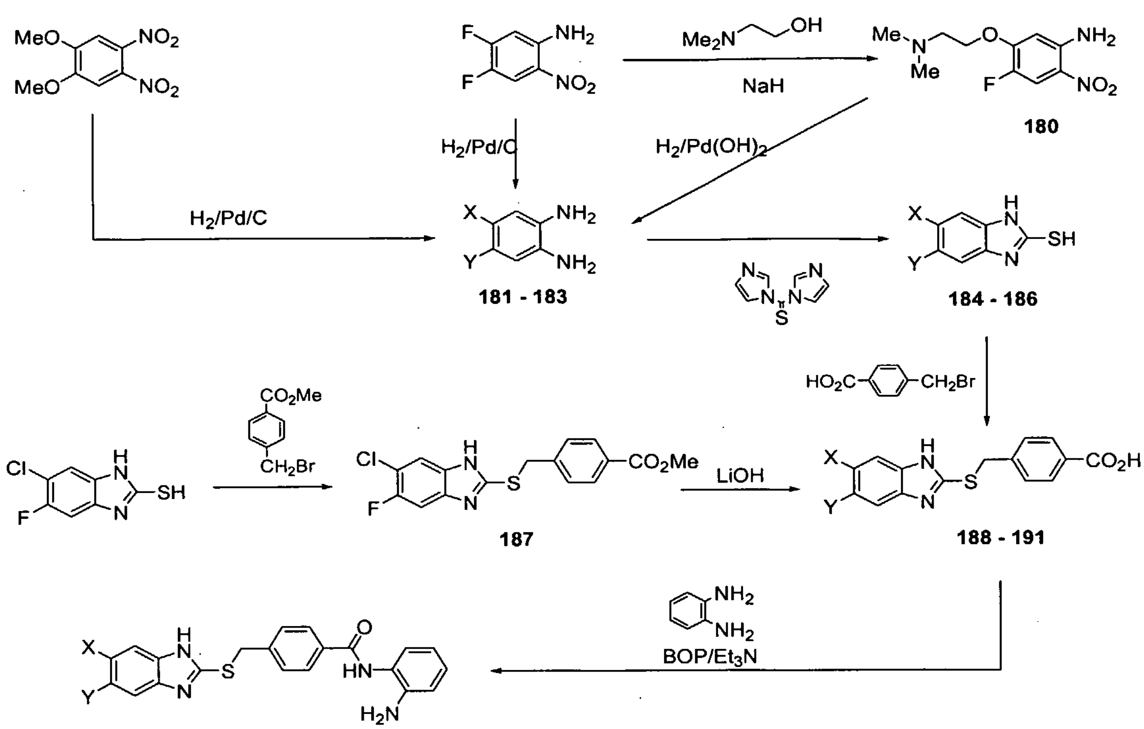
[0591] Step 3: 4-[(4-Pyridin-3-yl-thiazol-2-ylamino)-methyl]-benzoic acid (176):

[0592] The title compound **176** was obtained following the same procedure as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **174** as starting material (27% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 8.99 (dd, J= 2.0, 0.8, 1H), 8.42 (dd, J= 4.7, 1.6 Hz, 1H), 8.23 (t, J= 5.9 Hz, 1H), 8.11 (dt, J= 8.2, 2.0 Hz, 1H), 7.76 (d,J= 8.2 Hz, 2H), 7.36 (ddd, J= 7.8, 4.7, 0.8 Hz, 1H), 7.23 (d, J= 8.2 Hz, 2H), 7.21 (s, 1H), 7.47 (d, J= 5.5 Hz, 2H). m/z: 312.3 (MH^+).

[0593] Step 4: N-(2-Amino-phenyl)-4-[(4-pyridin-3-yl-thiazol-2-ylamino)-methyl]-benzamide (179)

[0594] The title compound **179** was obtained following the same procedures as the BOP coupling described in scheme 1, step 5 (example 1) using compound **176** as starting material (94% yield). ^{1}H NMR ($CDCl_3$) δ(ppm): 10.00 (s, 1H), 9.00 (dd, J= 3.1, 0.8 Hz, 1H), 8.43 (dd, J= 4.7, 1.6 Hz, 1H), 8.33 (t, J= 6.3 Hz, 1H), 8.11 (dt, J= 7.8, 2.3 Hz, 1H), 7.89 (d, J= 8.6 Hz, 2H), 7.62 (dd, J= 5.9, 3.5 Hz, 1H), 7.50 (d, J= 8.6 Hz, 2H), 7.37 (dd, J= 7.8, 4.7 Hz, 1H), 7.26 (dd, J= 5.5, 3.5 Hz, 1H), 7.24 (s, 1H), 4.56 (d, J= 5.9 Hz, 2H). m/z: 402.1 (MH^+).

Scheme 38



192: Example 91
193: Example 92
194: Example 93
195: Example 94

Compounds	Example	X	Y
181, 184, 188, 192	91	$(CH_3)_2NCH_2CH_2O$-	F
182, 185, 189, 193	92	CH_3O-	CH_3O-
183, 186, 190, 194	93	F	F
191, 195	94	Cl	F

Example 91

N-(2-Amino-phenyl)-4-[6-(2-dimethylamino-ethoxy)-5-fluoro-1*H*-benzoimidazol-2-ylsulfanylmethyl]-benzamide (192)

[0595] Step 1: 5-(2-Dimethylamino-ethoxy)-4-fluoro-2-nitro-phenylamine (180):

[0596] A flame-dried round-bottomed flask was charged with 4,5-difluoro-2-nitroaniline (2.00g, 11.49 mmol) and *N,N*-dimethylethanolamine. Pyridine (44 mL) was added followed by slow addition of NaH (60% in mineral oil, 965mg, 24.1 mmol). The mixture was put under N_2 atmosphere, stirred at rt for 16 h and quenched with H_2O. Solvents were removed *in vacuo* and the residue was partitioned between H_2O and EtOAc. The organic layer was extracted twice with HCl 1N, the combined acidic extracts were neutralized with saturated $NaHCO_3$ to form a precipitate which was allowed to stand overnight, collected by filtration and purified by flash

chromatography using MeOH/$CHCl_3$ with increasing polarity (10:90 to 15: 85) to afford the title compound **180** (1.30g, 47% yield). ^{1}H NMR: (CD_3OD) δ (ppm): 7.76 (d, J= 11.7 Hz, 1H), 6.53 (d, J= 7.4 Hz, 1H), 4.19 (t, J= 5.5 Hz, 2H), 2.84 (t, J= 5.5 Hz, 2H), 2.37 (s, 6H). m/z: 244.2 (MH^+).

[0597] Step 2: 4-(2-Dimethylamino-ethoxy)-5-fluoro-benzene-1,2-diamine (181):

[0598] A solution of intermediate **180** (220mg, 0.904 mmol) in acetic acid (3.6 mL) was degassed and put under N_2 atmosphere. A catalytic amount of $Pd(OH)_2$ was added and the black mixture was hydrogenated (1 atm) at rt for 16 h, filtered through a celite pad and rinsed with MeOH. The filtrate was concentrated *in vacuo* at 80°C to afford the title compound **181** as a mixture with $AcONHEt_3$ (252mg, 75%). ^{1}H NMR: (CD_3OD) δ (ppm): 6.54 (d, J= 7.8 Hz, 1H), 6.51 (d, J= 12.3 Hz, 1H), 4.21 (t, J= 5.1 Hz, 2H), 3.40 (t, J= 5.1 Hz, 2H), 2.89 (s, 6H). m/z: 214.1 (MH^+).

[0599] Step 3: 6-(2-Dimethylamino-ethoxy)-5-fluoro-1H-benzoimidazole-2-thiol (184):

[0600] The title compound **184** was obtained following the procedure described in *J.Med.Chem.*, **1998**, *63*, 977-983, starting from the compound **181** (96% yield). ^{1}H NMR: (CD_3OD) δ(ppm): 7.16 (d, J= 1.2 Hz, 0.5H), 7.07 (d, J= 10.4 Hz, 1H), 7.04 (d, J= 7.2 Hz, 0.5H), 4.37 (t, J= 4.9 Hz, 2H), 3.50 (t, J= 5.1 Hz, 2H), 2.92 (s, 6H). m/z: 256.2 (MH^+).

[0601] Step 4: 4-[6-(2-Dimethylamino-ethoxy)-5-fluoro-1H-benzoimidazol-2-ylsulfanylmethyl]-benzoic acid (188):

[0602] The title compound **188** was obtained following same procedure as for the alkylation described in scheme 27, step 1 (examples 66 and 67) reacting compound **184** with □-bromo-toluic acid (100% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 12.65 (s, 1H), 7.92 (s, 1H), 7.83 (d, J= 8.2 Hz, 2H), 7.51 (d, J= 8.0 Hz, 2H), 7.30-7.27 (m, 1H), 4.58 (s, 2H), 4.40 (t, J= 4.9 Hz, 2H), 3.54 (t, J= 4.9 Hz, 2H), 2.88 (s, 6H). m/z: 390.2 (MH^+).

[0603] Step 5: N-(2-Amino-phenyl)-4-[6-(2-dimethylamino-ethoxy)-5-fluoro-1H-benzoimidazol-2-ylsulfanylmethyl]-benzamide (**192**)

[0604] The title compound **192** was obtained following the same procedure as for the BOP coupling described in scheme 1, step 5 (example 1) using compound **188** as starting material. (30% yield). ^{1}H NMR: (acetone-d_6) δ (ppm): 9.02 (bs, 1H), 7.95 (d, J= 8.0 Hz, 2H), 7.61 (d, J= 8.0 Hz, 2H), 7.27 (d, J= 7.6 Hz, 1H), 7.28-7.10 (m, 2H), 6.99 (td, J= 8.0, 1.6 Hz, 1H), 6.86 (dd, J= 7.8, 1.2 Hz, 1H), 6.66 (t, J= 8.8 Hz, 1H), 4.65 (s, 2H), 4.63 (bs, 2H), 4.22 (bs, 2H), 2.87 (bs, 2H), 2.41 (s, 6H). m/z: 480.4 (MH^+).

Example 92

N-(2-Amino-phenyl)-4-(5,6-dimethoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide (193)

[0605] Step 1: 4,5-Dimethoxy-benzene-1,2-diamine (182):

[0606] A solution of 1,2-dimethoxy-4,5-dinitrobenzene (500mg, 2.19 mmol) in MeOH (10 mL) was degassed and put under N_2 atmosphere. A catalytic amount of Pd on charcoal (10%) was quenched with MeOH (1 mL) and transferred in one shot as a suspension in MeOH into the solution. Acetic acid (1.5 mL) was added and the black mixture was put under H_2 atmosphere (1 atm), stirred at rt for 16 h. The mixture was filtered through a celite pad and rinsed with MeOH. The filtrate was concentrated *in vacuo* at 80°C to afford the title compound **182** (residual acetic acid could not be removed from the product). ^{1}H NMR: (DMSO-d_6) δ(ppm): 6.23 (s, 2H), 3.56 (s, 6H). m/z: 169.3. (MH^+).

[0607] Step 2: 5,6-Dimethoxy-1H-benzoimidazole-2-thiol (185):

[0608] The title compound **185** was obtained following the procedure described in *J.Med.Chem.*, **1998**, *63* ,977-983, starting from compound **182**. (44% yield for 2 steps). ^{1}H NMR: (DMSO-d_6) δ(ppm): 12.29 (s, 2H), 6.71 (s, 2H), 3.74 (s, 6H). m/z: 211.2 (MH^+).

[0609] Step 3: 4-(5,6-Dimethoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzoic acid (189):

[0610] The title compound **189** was obtained following same procedure as for the alkylation described in scheme 27, step 1 (example 66 and 67) reacting compound **185** with □-bromo-toluic acid (60% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 7.83 (d, J= 8.2 Hz, 2H), 7.43 (d, J= 8.4 Hz, 2H), 7.06 (s, 2H), 4.61 (s, 2H). m/z: 345.2 (MH^+).

[0611] Step 4: N-(2-Amino-phenyl)-4-(5,6-dimethoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide (193)

[0612] The title compound **193** was obtained following the same procedures as for the BOP coupling described in scheme 1, step 5 (example 1) using compound **189** as starting material. (148mg, 59% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 12.30 (s, 1H), 9.55 (s, 1H), 7.85 (d, J= 8.0 Hz, 2H), 7.48 (d, J= 8.4 Hz, 2H), 7.10 (d, J= 7.8 Hz, 2H), 6.92 (td, J= 7.2, 1.6 Hz, 1H), 6.91-6.85 (bs, 1H), 6.73 (dd, J= 8.2, 1.2 Hz, 1H), 6.55 (td, J= 7.8, 1.6 Hz, 1H), 4.85 (s, 2H), 4.52 (s, 2H), 3.74 (s, 6H). m/z: 435.5 (MH^+).

Example 93

N-(2-Amino-phenyl)-4-(5,6-difluoro-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide (194)

[0613] Step 1: 4,5-Difluoro-benzene-1,2-diamine (183):

[0614] The title compound **183** was obtained following the same procedure described as example 92, step 1 (scheme 38), but substituting 1,2-dimethoxy-4,5-dinitrobenzene for 4,5-difluoro-2nitroaniline (97% yield). ^{1}H NMR: (CD_3OD) δ (ppm): 6.53 (t, J=10.0 Hz, 2H). m/z: 145.3 (MH^+).

[0615] Step 2: 5,6-Difluoro-1H-benzoimidazole-2-thiol (186):

[0616] The title compound **186** was obtained following the procedure described in *J.Med.Chem.*, **1998**, *63*, 977-983 starting from compound **183** (60% yield). ^{1}H NMR: (CD_3OD) δ(ppm): 7.48 (s, 0.5H), 7.13 (d, J= 8.4 Hz, 1H), 7.11 (d, J= 6.4 Hz, 1H), 1.99 (s, 1.5H). m/z: 187.1 (MH^+).

[0617] Step 3: 4-(5,6-Difluoro-1H-benzoimidazol-2-ylsulfanylmethyl)-benzoic acid (190):

[0618] The title compound **190** was obtained following same procedure as for the alkylation described in scheme 27, step 1 (example 66 and 67) reacting compound **186** with □-bromo-toluic acid (59% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.07 (s, 0.5H), 7.84 (d, J= 8.0 Hz, 2H), 7.68 (s, 1.5H), 7.52 (d, J= 8.2 Hz, 2H), 5.53-5.45 (m, 2H), 4.60 (s, 2H).m/z: 321.2 (MH^+).

[0619] Step 4: N-(2-Amino-phenyl)-4-(5,6-difluoro-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide (194)

[0620] The title compound **194** was obtained following the same procedures as the BOP coupling described in scheme 1, step 5 (example 1) using compound **186** as starting material (39% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.59 (s, 1H), 7.88 (d, J= 8.0 Hz, 2H), 7.54 (d, J= 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.13 (d, J= 7.6 Hz, 1H), 6.95 (t, J= 7.6 Hz, 1H), 6.76 (d, J= 7.4 Hz, 1H), 6.58 (t, J= 7.4 Hz, 1H), 4.61 (s, 2H). m/z: 411.4 (MH^+).

Example 94

N-(2-Amino-phenyl)-4-(5-chloro-6-fluoro-1*H*-benzoimidazol-2-ylsulfanylmethyl)-benzamide (195)

[0621] Step 1: 4-(6-Chloro-5-fluoro-1H-benzoimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (187):

[0622] The title compound **187** was obtained following same procedure as for the alkylation described in scheme 27, step 1 (example 66 and 67) reacting 6-chloro-5-fluorobenzimidazole-2-thiol with methyl 4-(bromomethyl)benzoate (54% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): (parent, missing protons: 7.85 (d, J= 8.4 Hz, 2H), 7.55 (d, J= 8.4 Hz, 2H), 3.80 (s, 2H), 3.34 (s, 3H). m/z: 351.2 (MH^+).

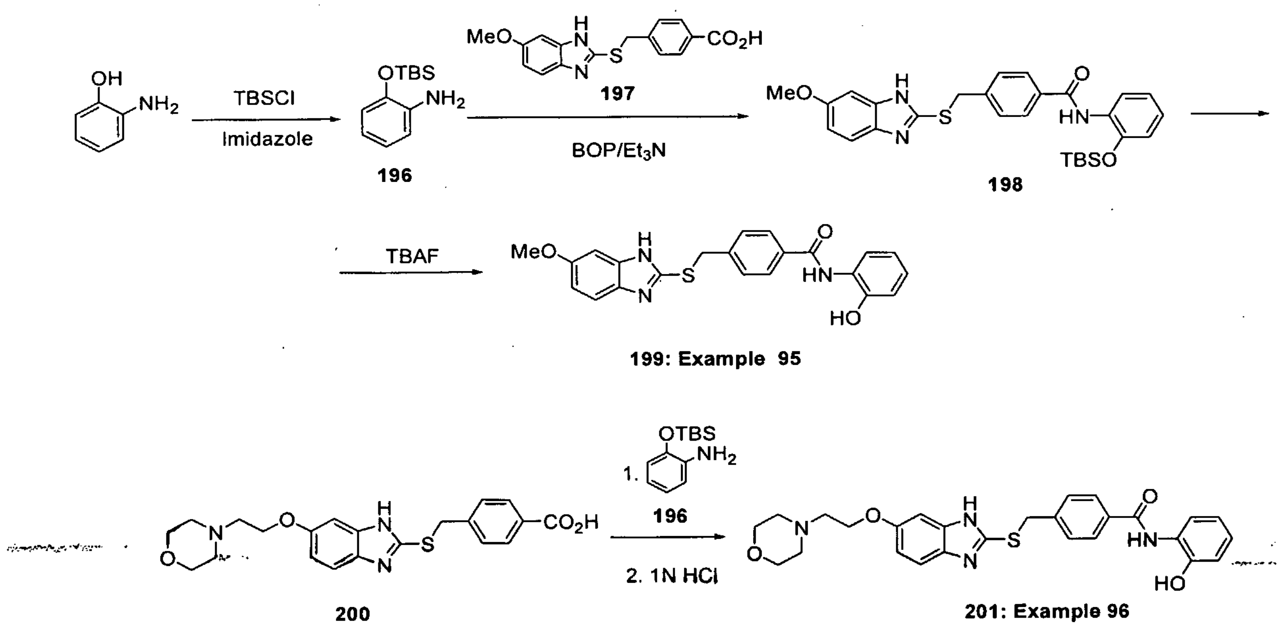
[0623] Step 2: 4-(5-Chloro-6-fluoro-1H-benzoimidazol-2-ylsulfanylmethyl)-benzoic acid (191):

[0624] The title compound **191** was obtained following the same procedure as for the hydrolysis described in scheme 1, step 4 (example 1) using compound **187** as starting material (83% yield). ^{1}H NMR: (DMSO-d$_6$) δ (ppm): 7.88 (d, J= 8.2 Hz, 2H), 7.67 (d, J= 6.8 Hz, 1H), 7.55 (d, J= 8.2 Hz, 2H), 7.53 (d, J= 6.8 Hz, 1H), 4.65 (s, 2H). m/z: 337.2 (MH$^+$).

[0625] Step 3: N-(2-Amino-phenyl)-4-(5-chloro-6-fluoro-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide (195)

[0626] The title compound **195** was obtained following the same procedures as the BOP coupling described in scheme 1, step 5 (example 1) using compound **191** as starting material (62% yield). ^{1}H NMR: (DMSO-d$_6$) δ (ppm): 12.87 (bs, 1H), 9.56 (s, 1H), 7.87 (d, J= 8.0 Hz, 2H), 7.62-7.57 (m, 1H), 7.53 (d, J= 8.2 Hz, 2H), 7.52-7.48 (m, 1H), 7.10 (d, J= 7.8 Hz, 1H), 6.92 (td, J= 8.0, 1.6 Hz, 1H), 6.73 (dd, J= 7.8, 1.4 Hz, 1H), 6.55 (t, J= 7.4 Hz, 1H), 4.86 (s, 2H), 4.61 (s, 2H). m/z: 427.4 (MH$^+$).

Scheme 39



EExample 95

***N*-(2-Hydroxy-phenyl)-4-(5-methoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide (199)**

[0627] Step 1: 2-(tert-Butyl-dimethyl-silanyloxy)-phenylamine (196):

[0628] To a stirred solution of 2-aminophenol (3.00g, 27.5 mmol) in DCM (150ml) was added *tert*-butyldimethylsilyl chloride (4.35ml, 28.9 mmol) and Et$_3$N (4.02ml, 28.9 mmol). The reaction mixture was stirred 16 h at room temperature. The organic phase was washed with water and

brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (5% AcOEt in hexane) to afford the title compound **196** (5.56g, 91% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.61 (s, 1H), 7.16 (s, 1H), 6.58 (s, 2H), 6.45 (s, 1H), 6.09 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.83 (s, 6H). m/z: 224.1 (MH^+).

[0629] Step 2: N-[2-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-4-(5-methoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide (198):

[0630] The title compound **198** was obtained following the same procedures as for the BOP coupling described in scheme 1, step 5 (example 1) reacting the compound **197** (described in the Patent Application WO 03/024448) with the compound **196**. m/z: 520.3 (MH^+).

[0631] Step 3: N-(2-Hydroxy-phenyl)-4-(5-methoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzamide (199)

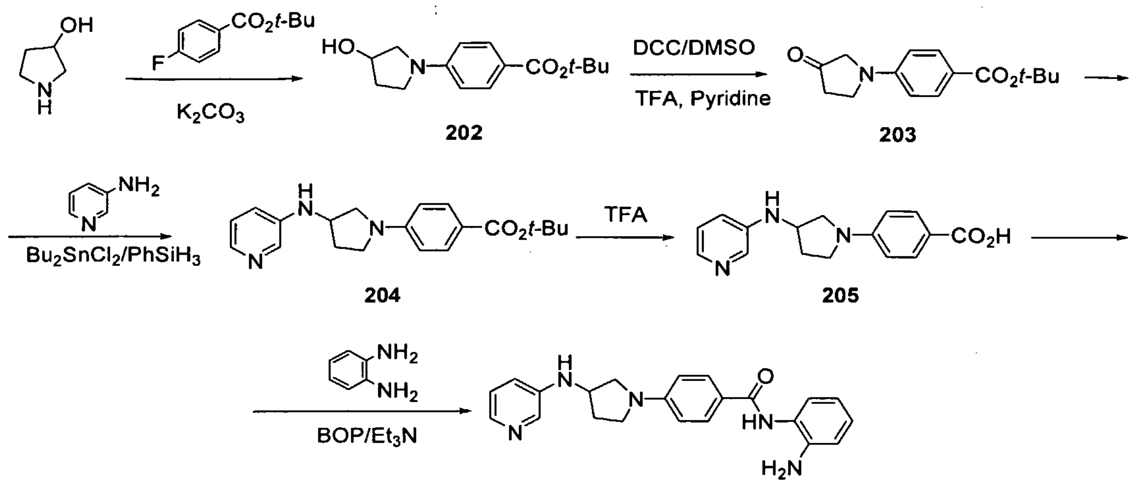
[0632] To a stirred solution of compound **198** (313mg, 0.600 mmol) in THF (15 ml) was added TBAF 1M in THF (1.20ml, 1.20 mmol). The reaction mixture was stirred 16 h at room temperature. The solvent was evaporated and the residue was dissolved in EtOAc, washed with sat. NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound **199** (150mg, 61% yield) as a white powder. ^{1}H NMR (DMSO-d_6) δ (ppm): 9.72 (bs, 1H), 9.49 (bs, 1H), 7.90 (d, J= 8.1 Hz, 2H), 7.63 (d, J= 8.1 Hz, 1H), 7.58 (d, J= 8.8 Hz, 2H), 7.51 (d, J= 9.5 Hz, 1H), 7.08-6.89 (m, 4H), 6.81 (dd, J= 7.0, 7.0 Hz, 1H), 4.76 (s, 2H), 3.81 (s, 3 H). m/z: 406.2 (MH^+).

Example 96

N-(2-Hydroxy-phenyl)-4-{[6-(2-morpholin-4-yl-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide (201)

[0633] Title compound **201** was obtained following the same procedures described in example 95 substituting compound **197** for compound **200** (described in the Patent Application WO 03/024448) and using 1N HCl instead of TBAF in the last step (26% yield). ^{1}H NMR: (CD_3OD) δ (ppm): 7.93 (d, J= 8.5 Hz, 2H), 7.79 (d, J= 7.5 Hz, 1H), 7.55 (d, J= 8.0 Hz, 2H), 7.33 (d, J= 8.5 Hz, 1H), 7.23 (s, 1H), 7.04 (t, J= 7.0 Hz, 1H), 6.92-6.85 (m, 3H), 7.40 (s, 2H), 4.14-4.12 (m, 2H), 3.72-3.70 (m, 4H), 2.81-2.79 (m, 2H), 2.62-2.60 (m, 4H). m/z: 505.5 (MH^+).

Scheme 40



206: Example 97

Example 97

N-(2-Amino-phenyl)-4-[3-(pyridin-3-ylamino)-pyrrolidin-1-yl]-benzamide (206)

[0634] Step 1: 4-(3-Hydroxy-pyrrolidin-1-yl)-benzoic acid tert-butyl ester (202):

[0635] The title compound **202** was obtained following the procedure described in *J. Heterocycl. Chem.*, **1994**, *31*, 1241, (91% yield). ^{1}H NMR: (CD_3OD) δ(ppm): 7.77 (d, J= 9.0 Hz, 2H), 6.54 (d, J= 9.0 Hz, 2H), 4.57-4.53 (m, 1H), 3.57-3.50 (m, 2H), 3.45 (td, J= 9.4, 3.3 Hz, 1H), 3.29 (dd, J= 12.7, 1.6 Hz, 1H), 2.22-2.13 (m, 1H), 2.10-2.03 (m, 1H), 1.59 (s, 9H). m/z: 264.4 (MH^+).

[0636] Step 2: 4-(3-Oxo-pyrrolidin-1-yl)-benzoic acid tert-butyl ester (203):

[0637] The title compound **203** was obtained following the procedure described in *J. Heterocycl. Chem.*, **1994**, *31*, 1241 (73% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 7.74 (d, J= 8.8 Hz, 2H), 6.67(d, J= 9.0 Hz, 2H), 3.75 (s, 2H), 3.69 (t, J= 7.4 Hz, 2H), 2.72 (t, J= 7.6 Hz, 2H), 1.52 (s, 9H). m/z: 262.4 (MH^+).

[0638] Step 3: 4-[3-(Pyridin-3-ylamino)-pyrrolidin-1-yl]-benzoic acid tert-butyl ester (204):

[0639] The title compound **204** was obtained following the procedure as for the reductive amination described in scheme 3, step 2 (example 12) starting from compound **203** and using 3-aminopyridine instead of 6-(pyridin-3-yl)pyridin-2-amine (**11**) (76% yield). ^{1}H NMR: (acetone-d_6) δ (ppm): 8.08 (d, J= 2.7 Hz, 1H), 7.85(dd, J= 4.3, 1.6 Hz, 1H), 7.79 (d, J= 9.0 Hz, 2H), 7.09 (ddd, J= 8.2, 4.5, 0.8 Hz, 1H), 7.06 (ddd, J= 8.2, 2.7, 1.6 Hz, 1H), 6.58 (d, J= 9.0 Hz, 2H), 4.33 (quint, J= 4.9 Hz, 1H), 3.79 (dd, J= 10.2, 6.1 Hz, 1H), 3.60-3.54 (m, 1H), 3.51-3.45 (m, 1H),

3.32 (dd, J= 7.2, 4.1 Hz, 1H), 2.44 (sext., J= 7.6 Hz, 1H), 2.18-2.11 (m, 1H), 1.56 (s, 9H). m/z: 340.4 (MH^+).

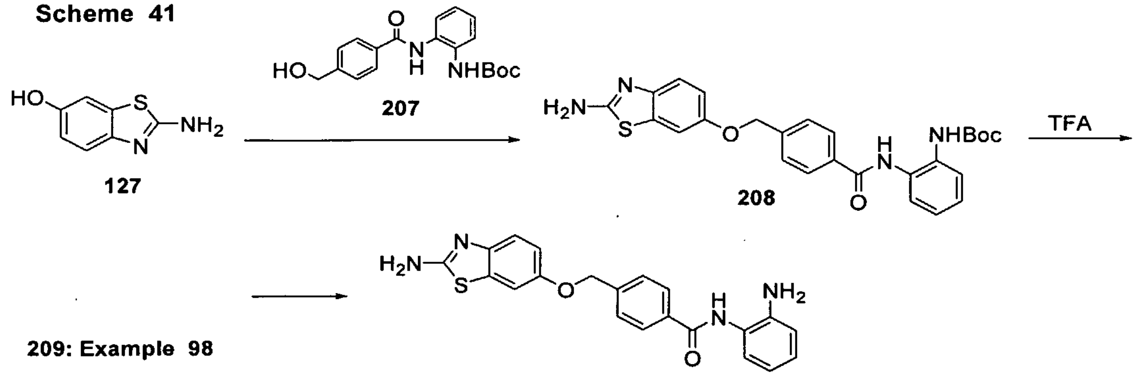
[0640] Step 4: 4-[3-(Pyridin-3-ylamino)-pyrrolidin-1-yl]-benzoic acid (205):

[0641] The title compound **205** was obtained following the same procedures as for the Boc cleavage described in scheme 28, step 5 (example 68) using compound **204** as starting material (96% yield). ^{1}H NMR: (DMSO-d_6) d (ppm): 8.09 (d, J= 2.0 Hz, 1H), 8.02(d, J= 3.5 Hz, 1H), 7.74 (d, J= 8.8 Hz, 2H), 7.68-7.62 (m, 2H), 7.29-7.26 (m, 1H), 6.57 (d, J= 8.8 Hz, 2H), 4.29-4.26 (m, 1H), 3.71 (dd, J= 10.6, 5.7 Hz, 1H), 3.51-3.42 (m, 2H), 3.23 (dd, J= 10.6, 3.5 Hz, 1H), 2.35 (sext., J= 7.2 Hz, 1H), 2.06-1.98 (m, 1H). m/z: 284.4 (MH^+).

[0642] Step 5: N-(2-Amino-phenyl)-4-[3-(pyridin-3-ylamino)-pyrrolidin-1-yl]-benzamide (206)

[0643] The title compound **206** was obtained following the same procedures as for the BOP coupling described in scheme 1, step 5 (example 1) using compound **205** as starting material (10% yield). ^{1}H NMR: (CD_3OD) δ(ppm): 8.14 (s, 1H), 7.96 (d, J= 2.3 Hz, 1H), 7.86 (d, J= 9.0 Hz, 2H), 7.77 (dd, J= 4.7, 1.4 Hz, 1H), 7.61-7.58 (m, 1H), 7.25 (dd, J= 6.1, 3.1 Hz, 1H), 7.18 (ddd, J= 8.4, 4.7, 0.8 Hz, 1H), 7.15 (dd, J= 8.0, 1.6 Hz, 1H), 7.11 (ddd, J= 8.2, 2.7, 1.4 Hz, 1H), 7.05 (td, J= 7.2, 1.4 Hz, 1H), 6.89 (dd, J= 8.0, 1.4 Hz, 1H), 6.76 (td, J= 7.6, 1.4Hz, 1H), 6.64 (d, J= 8.8 Hz, 2H), 4.26 (quint, J= 4.3 Hz, 1H), 3.78 (dd, J= 10.0, 6.1 Hz, 1H), 3.62-3.56 (m, 1H), 3.53-3.47 (m, 1H), 3.31-3.29 (m, 1H), 2.42 (sext., J= 7.4 Hz, 1H), 2.12-2.08 (m, 1H). m/z: 374.4 (MH^+).

Scheme 41



Example 98

4-(2-Amino-benzothiazol-6-yloxymethyl)-*N*-(2-amino-phenyl)-benzamide (209)

[0644] Step 1: {2-[4-(2-Amino-benzothiazol-6-yloxy)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (208):

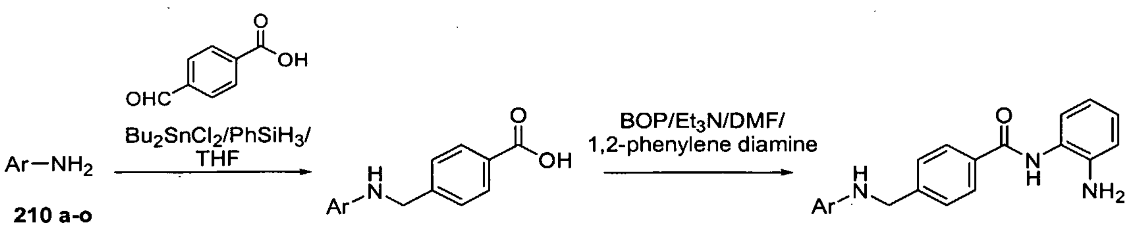
[0645] The title compound **208** was obtained following the same procedure as applied for the synthesis of compound **133** (scheme 32), using compound **207** (described in the Patent

Application WO 03/024448) instead of dimethylamino-ethanol and substituting compound **129** (scheme 32) for compound **127** (also mentioned in the scheme 32) (43% yield). ^{1}H NMR (DMSO-d_6) δ (ppm): 9.81 (s, 1H), 8.66 (s, 1H), 7.94 (d, J=8.4 Hz, 2H), 7.58 (d, J= 8.4 Hz, 2H), 7.51 (d, J= 8.2 Hz, 2H), 7.37 (d, J= 2.5 Hz 1H), 7.23 (d, J= 8.8 Hz, 1H), 7.18 (td, J=7.8, 1.8 Hz, 1H), 7.13 (td, J=7.6, 1.6 Hz, 1H), 6.89 (dd, J= 8.6, 2.5 Hz, 1H), 5.18 (s, 2H), 1.43 (s, 9H). m/z: 491.4 (MH$^+$).

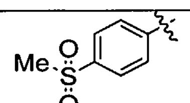
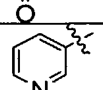
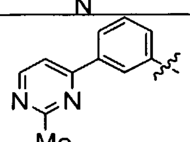
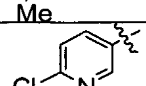
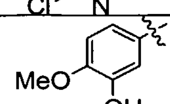
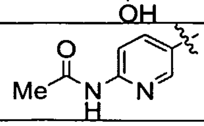
[0646] Step 2: N-(2-Amino-phenyl)-4-[3-(6-methoxy-benzothiazol-2-yl)-ureido]-benzamide (209)

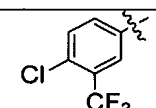
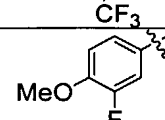
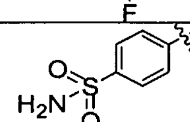
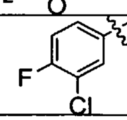
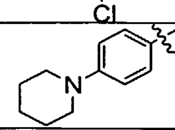
[0647] The title compound **209** was obtained following the same procedures as the Boc cleavage described in scheme 28, step 5 (example 68) using compound **208** as starting material. (28% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.63 (s, 1H), 7.96 (d, J= 8.2 Hz, 2H), 7.54 (d, J= 8.2 Hz, 2H), 7.37 (d, J= 2.5 Hz, 1H), 7.23 (s, 2H), 7.21 (d, J= 8.8 Hz, 1H), 7.14 (d, J= 8.0 Hz, 1H), 6.95 (td, J= 8.8, 2.3 Hz, 1H), 6.89 (dd, J= 8.6, 2.5 Hz, 1H), 6.75 (d, J= 6.7 Hz, 1H), 6.57 (t, J= 6.7 Hz, 1H), 5.16 (s, 2H), 4.89 (s, 2H). m/z: 391.4 (MH$^+$).

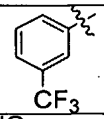
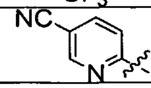
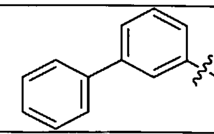
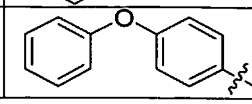
Scheme 42



210 a-o **211 a-o** **212 a-o: Examples 99-113**

Cmpds 210-212	Ex	Ar
212a	99	
212b	100	
212c	101	
212d	102	
212e	103	
212f	104	

Cmpds 210-212	Ex	Ar
212g	105	
212h	106	
212i	107	
212j	108	
212k	109	

Cmpds 210-212	Ex	Ar
212l	110	
212m	111	
212n	112	
212o	113	

Example 99:

***N*-(2-Amino-phenyl)-4-[(4-methanesulfonyl-phenylamino)-methyl]-benzamide (212a)**

[0648] Step 1: 4-[(4-Methanesulfonyl-phenylamino)-methyl]-benzoic acid (211a)

[0649] Title compound was obtained by reacting 4-methanesulfonyl-phenylamine (**210a**) with 4-formyl-benzoic acid, following the procedure described in the scheme 3, step 2 (example 12). ^{1}H NMR, (DMSO) δ (ppm): 7.87 (d, J= 7.6 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 6.64 (d, J = 8.0 Hz, 2H), 4.42 (s, 2H), 3.00 (s, 3H). LRMS: (calc.) 305.4; (obt.) 304.3 (MH)$^{+}$.

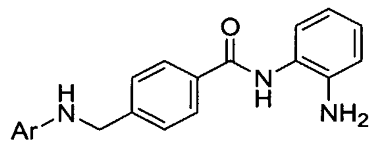
[0650] Step 2: N-(2-Amino-phenyl)-4-[(4-methanesulfonyl-phenylamino)-methyl]-benzamide (212a)

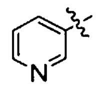
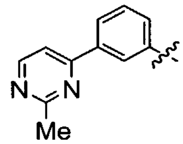
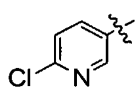
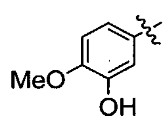
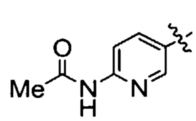
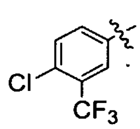
[0651] The compound was obtained by reacting the acid **211a** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1). ^{1}H NMR: (DMSO) δ (ppm): 9.57 (bs, 1H), 7.90 (d, J=8.4 Hz, 1H), 7.50 (d, J=8.2 Hz, 2H), 7.43 (d, J= 8.4 Hz, 2H), 7.35 (t, J=6.0 Hz, 1H), 7.11 (d, J=7.6 Hz, 1H), 6.93 (dt, J= 1.6, 8.0 Hz, 1H), 6.73 (dd, J=1.6, 8.0 Hz, 1H), 6.66 (d, J=8.8 Hz, 2H), 6.55 (dt, J=1.2, 7.6 Hz, 1H), 4.88 (bs, 2H), 4.43 (d, J=6.0 Hz, 2H). LRMS: (calc.) 395.5; (obt.) 396.4 (MH)$^{+}$.

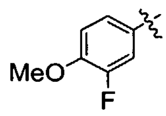
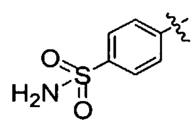
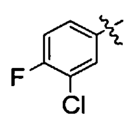
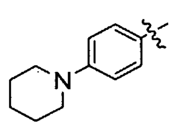
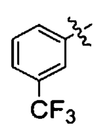
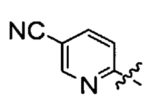
Examples 100-113:

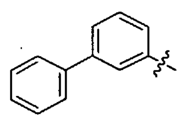
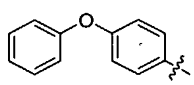
[0652] Examples 100-113 (compounds **212b-o**) were prepared using the same procedures as described for the compound **212a**, example 99 (scheme 42, table 1) starting from the arylamines **210b-o** via the intermediate acids **211b-o** (scheme 42).

Table 6

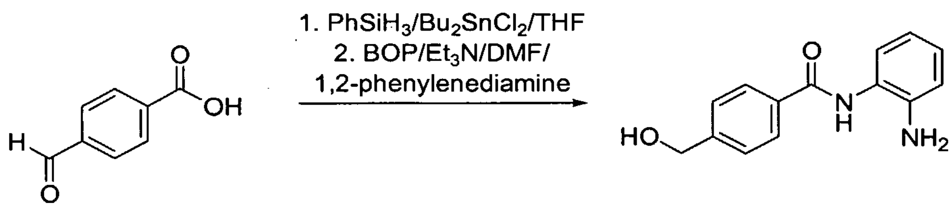


Ex.	Cmpd	Ar	Name	Characterization	Scheme
100	**212b**		N-(2-Amino-phenyl)-4-(pyridin-3-ylaminomethyl)-benzamide	**^{1}H NMR: (DMSO-d_6) δ(ppm):** 9.60 (bs, 1H), 7.98 (d, J=2.7 Hz, 1H), 7.92 (d, J=7.8 Hz, 2H), 7.82 (d, J= 4.3 Hz, 1H), 7.46 (d, J=8.2 Hz, 2H), 7.25 (dd, J=5.1, 4.7 Hz, 1H), 7.13 (d, J=7.8 Hz, 2H), 6.85 (dt, J= 1.5, 7.4 Hz, 1H), 6.75 (dd, J=1.6, 7.8 Hz, 1H), 6.58 (ddd, J=7.8, 7.0 Hz, 1H), 4.43 (s, 2H).	42
101	**212c**		N-(2-Amino-phenyl)-4-{[3-(2-methyl-pyrimidin-4-yl)-phenylamino]-methyl}-benzamide	**^{1}H NMR: ($CDCl_3$) δ(ppm):** 9.26 (bs, 1H), 8.34 (dd, J=1.8, 5.3 Hz, 1H), 7.59 (d, J=7.8 Hz, 2H), 7.37 (d, J= 4.9 Hz, 1H), 7.17 (d, J=8.2 Hz, 2H), 7.12 (s, 1H), 6.96 (d, J=8.0 Hz, 1H), 6.85 (t, J= 7.8 Hz, 1H), 6.80 (d, J=7.2 Hz, 1H), 6.62 (dd, J=6.0, 7.6 Hz, 1H), 6.43 (d, J=8.0 Hz, 1H), 6.38-6.33 (m, 1H), 6.25 (dd, J= 6.2, 7.6 Hz, 1H), 4.10 (s, 2H), 3.01 (s, 3H).	42
102	**212d**		N-(2-Amino-phenyl)-4-[(6-chloro-pyridin-3-ylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6) δ(ppm)**: 9.43 (bs, 1H), 7.77 (d, J=8.0 Hz, 2H), 7.56 (d, J=1.8 Hz, 1H), 7.30 (d, J= 8.2 Hz, 2H), 6.99-6.96 (m, 2H), 6.84-6.78 (m, 2H), 6.66 (t, J=6.2 Hz, 1H), 6.61 (d, 1H), 6.42 (t, J=7.4 Hz, 1H), 4.73 (s, 2H), 4.24 (d, J=6.3Hz, 2H).	42
103	**212e**		N-(2-Amino-phenyl)-4-[(3-hydroxy-4-methoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6) δ(ppm)**: 9.58 (bs, 1H), 8.58 (s, 1H), 7.90 (d, J=7.6 Hz, 2H), 7.43 (d, J=8.0 Hz, 2H), 7.14 (d, J=7.6 Hz, 1H), 6.95 (dd, J=6.8, 8.4 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 6.62-6.52 (m, 2H), 6.09 (d, J=2.4 Hz, 1H), 5.93-5.87 (m, 2H), 4.88 (s, 2H), 4.25 (d, J=6.0Hz, 2H), 3.60 (s, 3H).	42
104	**212f**		4-[(6-Acetylamino-pyridin-3-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide	**^{1}H NMR: (DMSO-d_6):** 9.98 (bs, 1H), 9.57 (bs, 1H), 7.88 (d, J=8.0 Hz, 2H), 7.70 (d, J=8.8 Hz, 1H), 7.62 (d, J= 2.8 Hz, 1H), 7.44 (d, J=8.0 Hz, 2H), 7.11 (d, J=7.6 Hz, 1H), 6.95-6.90 (m, 2H), 6.73 (d, J=8.0 Hz, 1H), 6.54 (t, J=7.6 Hz, 1H), 6.36 (t, J=6.0 Hz, 1H), 4.87 (s, 2H), 4.33 (d, J=6.0Hz, 2H), 1.97 (s, 3H).	42
105	**212g**		N-(2-Amino-phenyl)-4-[(4-chloro-3-trifluoromethyl-phenylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6):** 9.60 (bs, 1H), 7.92 (d, J=8.0 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 7.30 (d, J= 8.4 Hz, 1H), 7.12 (d, J=7.6 Hz, 1H), 7.05-6.91 (m, 2H), 6.79-6.74 (m, 2H), 6.56 (dd, J=6.8, 7.6 Hz, 1H), 4.88 (s, 2H), 4.40 (d, J=6.0Hz, 2H).	42

Ex.	Cmpd	Ar	Name	Characterization	Scheme
106	212h		N-(2-Amino-phenyl)-4-[(3-fluoro-4-methoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6):** 9.56 (bs, 1H), 7.89 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.0 Hz, 2H), 7.12 (d, J= 7.6 Hz, 1H), 6.93 (dt, J=1.2, 8.0 Hz, 1H), 6.85 (t, J=8.8 Hz, 1H), 6.74 (d, J= 7.6 Hz, 1H), 6.56 (t, J=7.6 Hz, 1H), 6.40 (dd, J=2.4, 14.0 Hz, 1H), 6.28 (bd, J=10.0 Hz, 1H), 6.23 (t, J= 6.4 Hz, 1H), 4.87 (s, 2H), 4.28 (s, 2H).	42
107	212i		N-(2-Amino-phenyl)-4-[(4-methanesulfonyl-phenylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6):** 9.55 (bs, 1H), 7.88 (d, J=8.0 Hz, 2H), 7.45-7.40 (m, 4H), 7.12-7.07 (m, 1H), 6.92 (dd, J=1.6, 8.8 Hz, 1H), 6.87 (s, 2H), 6.73 (dd, 1H), 6.59 (d, J=8.8 Hz, 2H), 6.53 (t, J=7.6 Hz, 1H), 4.85 (bs, 2H), 4.41 (d, J=6.4 Hz, 2H).	42
108	212j		N-(2-Amino-phenyl)-4-[(3-chloro-4-fluoro-phenylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6):** 9.58 (bs, 1H), 7.90 (d, J=8.0 Hz, 2H), 7.41 (d, J=8.4 Hz, 2H), 7.12 (d, J= 6.4 Hz, 1H), 7.08 (t, J=9.2 Hz, 1H), 6.94 (dt, J=1.6, 8.0 Hz, 1H), 6.75 (dd, J= 1.6, 8.0 Hz, 1H), 6.63-6.60 (m, 1H), 6.58-6.48 (m, 3H), 4.87 (bs, 2H), 4.32 (d, J=6.0 Hz, 2H).	42
109	212k		N-(2-Amino-phenyl)-4-[(4-piperidin-1-yl-phenylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6):** 9.56 (bs, 1H), 7.88 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.0 Hz, 2H), 7.12 (d, J= 8.0 Hz, 1H), 6.94 (t, J=7.3 Hz, 1H), 6.74 (d, J=8.0 Hz, 1H), 6.68 (d, J= 8.0 Hz, 2H), 6.56 (t, J=8.0 Hz, 1H), 6.45 (d, J=8.8 Hz, 2H), 4.86 (bs, 2H), 4.27 (d, J=6.0 Hz, 2H), 2.84-2.82 (m, 4H), 1.61-1.55 (m, 4H), 1.46-1.43 (m, 2H).	42
110	212l		N-(2-Amino-phenyl)-4-[(3-trifluoromethyl-phenylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6):** 9.58 (bs, 1H), 7.91 (d, J=8.0 Hz, 2H), 7.45 (d, J=8.4 Hz, 2H), 7.22 (dd, J=7.6, 8.4 Hz, 1H), 7.13 (d, J=6.8 Hz, 1H), 6.93 (dt, J=1.6, 8.0 Hz, 1H), 6.86-6.83 (m, 2H), 6.78 (dd, J=2.0, 8.0 Hz, 2H), 6.75 (dd, J=1.6, 8.0 Hz, 1H), 6.56 (dt, J=1.6, 7.6 Hz, 1H), 4.87 (bs, 2H), 4.40 (d, J=6.4 Hz, 2H).	42
111	212m		N-(2-Amino-phenyl)-4-[(5-cyano-pyridin-2-ylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO-d_6):** 9.57 (bs, 1H), 8.36 (d, J=2.0 Hz, 1H), 8.17 (t, J=6.4 Hz, 1H), 7.90 (d, J=8.0 Hz, 2H), 7.68 (dd, J=2.0, 8.8 Hz, 1H), 7.39 (d, J=8.0 Hz, 2H), 7.13 (d, J=8.0 Hz, 1H), 6.94 (t, J=8.4 Hz, 1H), 6.75 (dd, J=1.2, 7.6 Hz, 1H), 6.60-6.54 (m, 2H), 4.87 (bs, 2H), 4.61 (d, J=5.6 Hz, 2H).	42

Ex.	Cmpd	Ar	Name	Characterization	Scheme
112	**212n**		*N*-(2-Amino-phenyl)-4-(biphenyl-3-ylaminomethyl)-benzamide	**^{1}H NMR: (Acetone-d_6) δ(ppm):** 8.62 (s, 1H), 8.40-8.37 (m, 1H), 7.86 (d, J= 8.4 Hz, 2H), 7.58 (d, J= 8.2 Hz, 2H), 7.54 (dd, J= 8.6, 1.4 Hz, 2H), 7.39 (t, J= 7.2 Hz, 2H), 7.30 (d, J= 7.2 Hz, 1H), 7.17 (t, J= 7.6 Hz, 1H), 7.11 (td, J= 7.8, 1.6 Hz, 1H), 7.06 (td, J= 7.6, 1.6 Hz, 1H), 6.93 (t, J= 2.0 Hz, 1H), 6.87 (d, J= 6.7 Hz, 1H), 6.76 (dd, J= 7.6, 1.6 Hz, 1H), 6.66 (ddd, J= 8.2, 2.3, 1.0 Hz, 1H), 4.55 (s, 2H).	42
113	**212o**		*N*-(2-Amino-phenyl)-4-[(4-phenoxy-phenylamino)-methyl]-benzamide	**^{1}H NMR: (Acetone-d_6) δ(ppm):** 9.06 (bs, 1H), 7.99 (d, J= 8.2 Hz, 2H), 7.55 (d, J= 8.4 Hz, 2H), 7.28 (dd, J= 8.8, 7.2 Hz, 2H), 7.02-6.97 (m, 1H), 6.86 (dd, J= 8.8, 1.0 Hz, 2H), 6.83 (d, J= 9.0 Hz, 2H), 6.70 (d, J= 8.6 Hz, 2H), 6.69 (quint, J= 7.4 Hz, 1H), 4.65 (bs, 2H), 4.47 (s, 2H).	42

Scheme 43



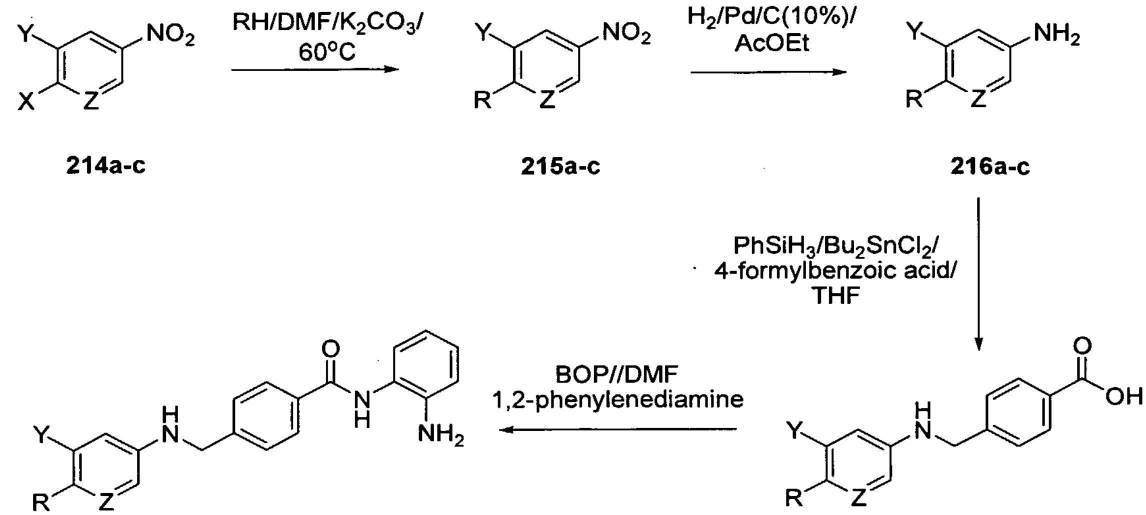
213: Example 114

Example 114:

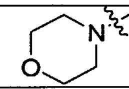
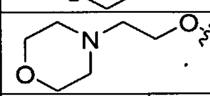
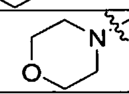
N-(2-Amino-phenyl)-4-hydroxymethyl-benzamide (213)

[0653] In a flask containing 4-formylbenzoic acid (300mg, 1.8 mmol) was added dibutyltin dichloride (55 mg, 0.18 mmol), followed by THF (5 ml) and phenylsilane (0.187 ml, 1.8 mmol). The resulting mixture was stirred overnight at room temperature under nitrogen, concentrated and used for the next step (coupling with o-phenylene-diamine) without further purification, following the procedures described in the scheme 1, step 5 (example 1), to afford the compound **213** (378 mg, 78% yield). ^{1}H NMR: (DMSO) δ (ppm): 9.63 (s, 1H), 7.94 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.5 Hz, 2H), 7.16 (d, J= 7.5 Hz, 1H), 6.96 (t, J=7.0 Hz, 1H), 6.78 (d, J=6.5, 1H), 6.59 (dd, J=7.0, 7.5 Hz, 1H), 4.88 (s, 1H), 4.57 (s, 2H). LRMS: (calc.) 242.3; (obt.) 243.4 $(MH)^+$.

Scheme 44



218a-c: Examples 115-117

Compound	Example	X	Y	Z	R
218a	115	F	F	CH	
218b	116	F	H	CH	
218c	117	Br	H	N	

Example 115:

N-(2-Amino-phenyl)-4-[(3-fluoro-4-morpholin-4-yl-phenylamino)-methyl]-benzamide (218a)

[0654] Step 1: 4-(2-Fluoro-4-nitro-phenyl)-morpholine (215a)

[0655] To a solution of **214a** (3 g, 18.85 mmol) in DMF (20 mL) were added morpholine (1.6ml, 18.85 mmol) and K_2CO_3 (10.4 g, 75.4 mmol) at room temperature. The reaction mixture was heated at 60 °C for 16 h, cooled, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluent with AcOEt/hexane (40:60) to afford title compound **215a** as a white solid (4.0 g, 89% yield). LRMS: 226.2 (calc.); 227.3 (obt.) $(MH)^+$.

[0656] Step 2: 3-Fluoro-4-morpholin-4-yl-phenylamine (216a)

[0657] Title compound **216a** was obtained by catalytic hydrogenation of nitro compound **215a**, following the procedure described in the scheme 38, step 1 (example 92) (92% yield). LRMS: 196.2 (calc.); 197.2 (obt.) $(MH)^+$.

[0658] Step 3: 4-[(3-Fluoro-4-morpholin-4-yl-phenylamino)-methyl]-benzoic acid (217a)

[0659] Title compound **226a** was obtained via a reaction of 4-formylbenzoate with amine **216a**, following the procedure described in the scheme 3, step 2 (example 12) (91% yield). LRMS: 330.4 (calc.); 331.5 (obt.) $(MH)^+$.

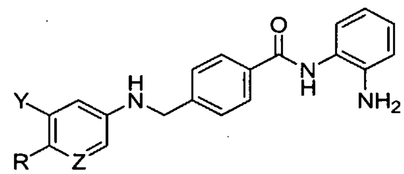
[0660] Step 4: N-(2-Amino-phenyl)-4-[(3-fluoro-4-morpholin-4-yl-phenylamino)-methyl]-benzamide (218a)

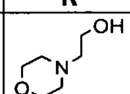
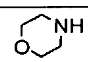
[0661] Title compound **218a** was obtained reacting acid **217a** with 1,2-phenylenediamine following the procedures described in the scheme 1, step 5 (example 1) (40% yield). ^{1}H NMR: (DMSO) δ (ppm): 9.57 (s, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.44 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5; 7.0 Hz, 1H), 6.82-6.74 (m, 2H), 6.57 (dd, J=7.0; 7.5 Hz, 1H), 6.37-6.30 (m, 2H), 4.86 (bs, 2H), 4.30 (d, J=5.71 Hz, 2H), 3.66 (bs, 4H), 2.80 (bs, 4H). LRMS: (calc.) 420.2; (obt.) 421.2 $(MH)^+$.

Examples 116 -117 (compounds 218b-c):

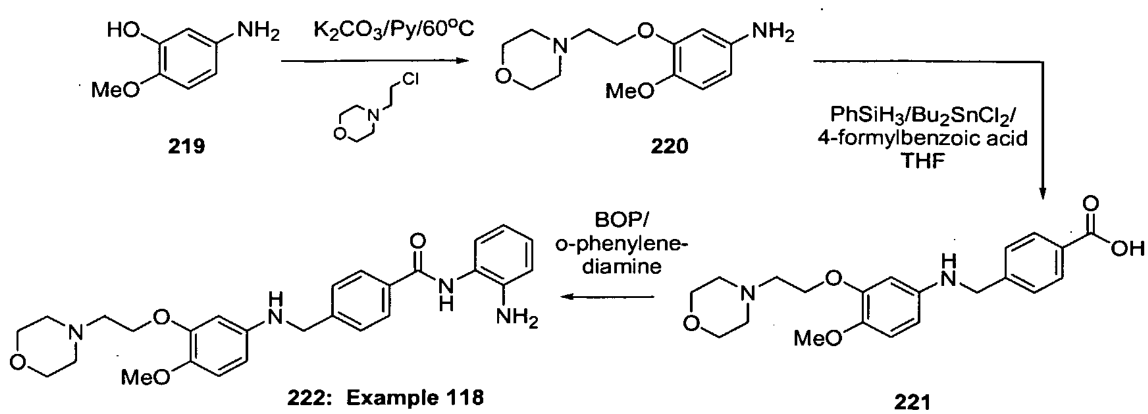
[0662] Examples 116-117 (compounds **218b-c**) were prepared using the same procedures as described for the compound **218a** (example 116, scheme 44) (table 3).

Table 7



Ex	Cmpd	R	Y	Z	Name	Characterization	Scheme
117	**218b**		H	CH	N-(2-Amino-phenyl)-4-{[4-(2-morpholin-4-yl-ethoxy)-phenylamino]-methyl}-benzamide	**^{1}H NMR: (DMSO-d_6) δ(ppm):** 9.64 (bs, 1H), 7.97 (d, J=8.4 Hz, 2H), 7.52 (d, J=7.9 Hz, 2H), 7.20 (d, J= 7.5 Hz, 1H), 7.02 (dd, J=7.0, 7.5 Hz, 1H), 6.83 (d, J=7.91, 1H), 6.77 (d, J=8.8 Hz, 2H), 6.65 (t, J= 7.5 Hz, 1H), 6.57 (d, J=8.8 Hz, 2H), 4.36 (bs, 2H), 4.07 (bs, 2H), 3.72 (bs, 4H), 3.00 (bs, 2H), 2.82 (bs, 4H).	44
118	**218c**		H	N	N-(2-Amino-phenyl)-4-[(6-morpholin-4-yl-pyridin-3-ylamino)-methyl]-benzamide	**^{1}H NMR: ($CDCl_3$) δ(ppm):** 9.59 (bs, 1H), 7.91 (d, J=8.3 Hz, 2H), 7.57 (d, J=2.9 Hz, 1H), 7.46 (d, J= 8.3 Hz, 2H), 7.14 (d, J=8.3 Hz, 1H), 7.97-6.93 (m, 2H), 6.76 (d, J=7.8 Hz, 1H), 6.64 (d, J= 8.8 Hz, 1H), 6.58 (t, J=7.8 Hz, 1H), 4.88 (bs, 2H), 4.30 (d, J= 5.8 Hz, 2H), 3.66-3.64 (m, 4H), 3.16-3.14 (m, 4H).	44

Scheme 45



Example 118:

N-(2-Amino-phenyl)-4-{[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenylamino]-methyl}-benzamide (222)

[0663] Step 1: 4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenylamine (220)

[0664] To a solution of 4-(2-chloro-ethyl)-morpholine (2.67 g, 14.4 mmol) in a solvent mixture pyridine (5 mL) and DMF (15 ml) were added amine **219** (2.00, 14.4 mmol) and K_2CO_3 (7.96 g, 57.6 mmol) at room temperature. The reaction mixture was heated at 60°C overnight, cooled, filtered and concentrated in *vacuo*. The residue was purivied by flash chromatography on silica gel eluting with 70:30 AcOEt/hexane to afford title compound **229** (3.6 g, 100% yield). LRMS: 252.3(calc.); 253.3 (obt.) $(MH)^+$.

[0665] Step 2: 4-{[4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenylamino]-methyl}-benzoic acid (221)

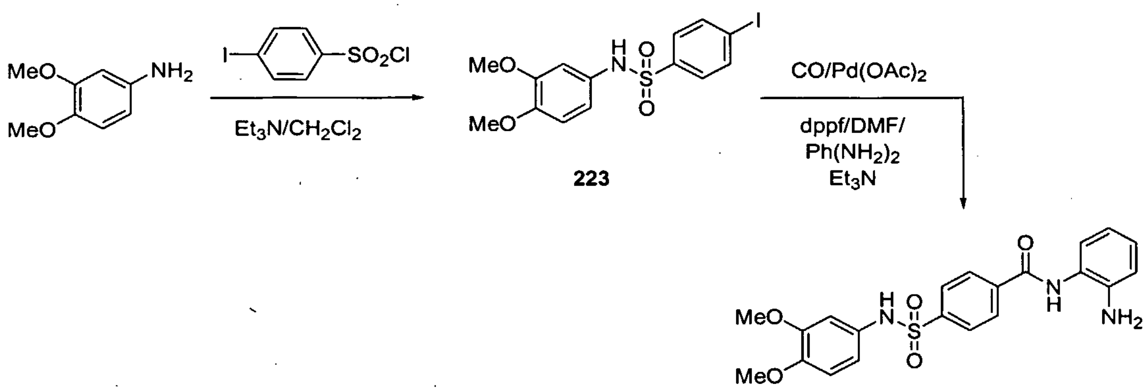
[0666] Title compound **221** was obtained reacting 4-formylbenzoate with amine **220**, following the procedure described in the scheme 3, step 2 (example 12) (1.9g, 99% yield). LRMS: 386.4(calc.); 387.4(obt.) $(MH)^+$.

[0667] Step 3: N-(2-Amino-phenyl)-4-{[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenylamino]-methyl}-benzamide (222)

[0668] Title compound **222** was obtained by coupling of the acid **221** (5.07mmol) with 1,2-phenylenediamine (5.07mmol) following the procedure described in the scheme 1, step 5 (example 1) (260mg, 11% yield). ^1H NMR: (DMSO) δ (ppm): 9.59 (s, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.9 Hz, 1H), 6.96 (dd, J = 8.5; 6.5 Hz, 1H), 6.77 (d, J=8.5 Hz, 1H), 6.65 (d, J=8.5 Hz, 1H), 6.58 (t, J=7.5 Hz, 1H), 6.31 (d, J=2.5 Hz, 1H), 6.03 (d, J=8.5

Hz, 1H), 4.86 (bs, 2H), 4.30 (d, J=5.5 Hz, 2H), 3.95 (dd, J=5.9, 5.5 Hz, 2H), 3.59 (s, 3H), 3.56 (bs, 4H), 2.63 (bs, 2H), 2.44 (bs, 4H).. LRMS: 476.6(calc.); 477.6(obt.) $(MH)^+$.

Scheme 46



224: Example 119

Example 119:

***N*-(2-Amino-phenyl)-4-(3,4-dimethoxy-phenylsulfamoyl)-benzamide (224)**

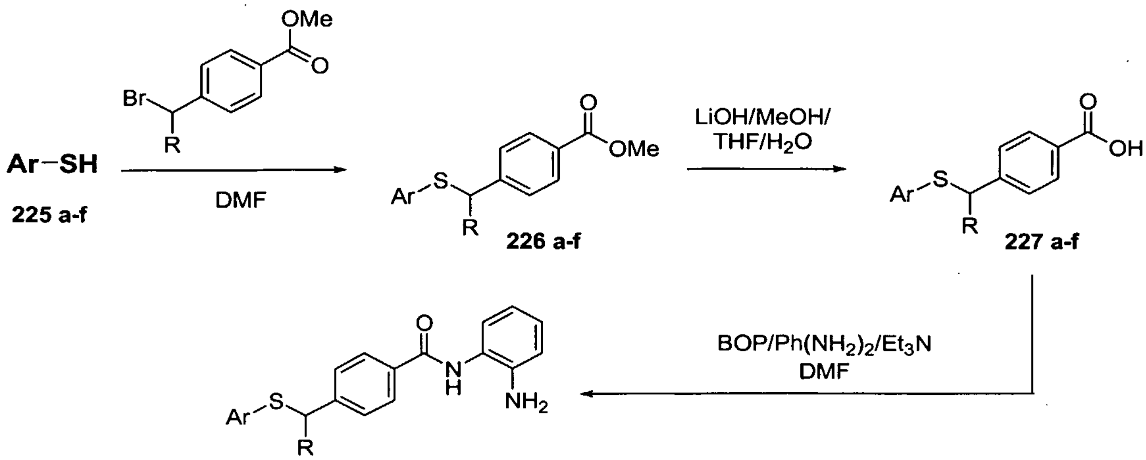
[0669] Step 1: N-(3,4-Dimethoxy-phenyl)-4-iodo-benzenesulfonamide (223)

[0670] The title compound 223 was obtained following the procedure described in the Patent application No WO 01/38322 A1, by reacting 3,4-dimethoxy-phenylamine with 4-iodo-benzenesulfonyl chloride (80% yield). LRMS: 419.2(calc.); 420.2(obt.) $(MH)^+$.

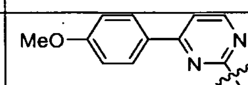
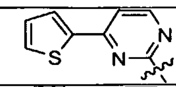
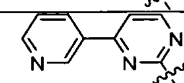
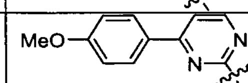
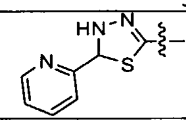
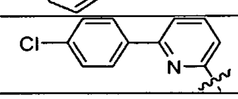
[0671] Step 2: N-(2-Amino-phenyl)-4-(3,4-dimethoxy-phenylsulfamoyl)-benzamide (224)

[0672] A mixture of **223** (705 mg, 1.7 mmol), 1,2-phenylenediamine (199 mg, 1.84 mmol), $Pd(OAc)_2$ (0.25 mmol, 15%) and 1,1'-bis (diphenylphosphino) ferrocene (160 mg, 0.29 mmol) was suspended in degassed DMF (10mL), treated with Et_3N (700 µL, 5.04 mmol), heated under CO atmosphere (balloon) for 18 h at 70°C. After evaporation of the DMF in *vacuo*, the residue was purified by flash chromatography (eluent AcOEt:hexane, 3:1) to give the title compound **224** (100 mg, 14 % yield). ^{1}H-NMR (CD_3OD-*d4*), δ (ppm): 10.05 (s, 1H), 9.76 (s, 1H), 8.06 (d, J=8.3 Hz, 2H), 7.79 (d, J=7.8 Hz, 2H), 7.11 (bs, 1H), 6.94 (bs, 1H), 6.77-6.69 (m, 3H), 6.54 (bs, 2H), 4.91 (bs, 2H), 3.62 (s, 3H).

Scheme 47



228 a-f: Examples 120-125

Compounds 225-228	Example	R	Ar
a	120	H	
b	121	H	
c	122	Me	
d	123	Me	
e	124	H	
f	125	H	

Example 120:

***N*-(2-Amino-phenyl)-4-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-benzamide (228a)**

[0673] Step 1: 4-[4-(4-Methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-benzoic acid methyl ester (226a)

[0674] To a solution of 4-(4-methoxy-phenyl)-pyrimidine-2-thiol (**225a**) (1.00 g, 4.58 mmol) in DMF (30 mL) was added 4-bromomethyl-benzoic acid methyl ester (1.05 g, 4.58 mmol). The mixture was heated at 60°C for 1h and evaporated to dryness to form the compound **226a,** which was used in the next without purification. LRMS = 366.4(calc.), 367.4 (found).

[0675] Step 2: 4-[4-(4-Methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-benzoic acid (227a)

[0676] To a stirred solution of **226a** (4.58mmol) in THF (20 ml) and MeOH (20ml) at room temperature was added a solution of LiOH-H_2O (960mg, 22.9 mmol) in water (50 ml). The reaction mixture was stirred 18 h at room temperature, diluted in water and acidified with 1N HCl (pH 5-6) to form a precipitate which was collected by filtration, washed with water and dried to afford the title compound **227a** (1.64 g, 99% yield). LRMS (calc.): 352.4, (found): 353.4.

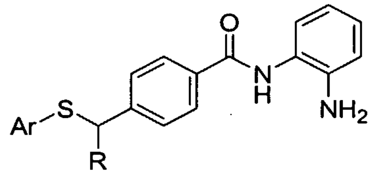
[0677] Step 3: N-(2-Amino-phenyl)-4-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-benzamide (228a)

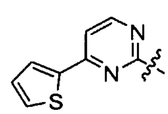
[0678] The title compound **228a** was obtained by coupling of acid **227a** with 1,2-phenylenediamine following the procedures described in the scheme 1, step 5 (example 1) (80% yield). ^{1}H NMR: (DMSO) δ (ppm): 9.57 (bs, 1H), 8.59 (d, J=5.5 Hz, 2H), 8.16 (d, J=7.0 Hz, 2H), 7.88 (d, J= 8.2 Hz, 2H), 7.70 (d, J=5.0 Hz, 1H), 7.57 (d, J=8.2, 2H), 7.12-7.07 (m, 2H), 6.93 (dd, J=8.2, 7.0 Hz, 1H), 6.73 (dd, J= 8.2, 1.6 Hz, 1H), 6.55 (dt, J=8.6, 1.1 Hz, 1H), 4.86 (bs, 2H), 4.55 (s, 2H), 3.83 (s, 3H) LRMS: (calc.) 442.5; (obt.) 443.5 $(MH)^+$.

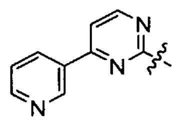
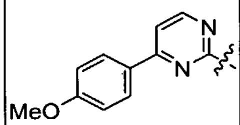
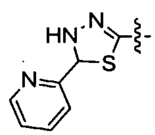
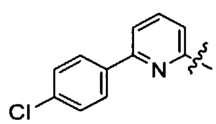
Examples 121-125:

[0679] Examples 121-125 (compounds **228b-f**) were prepared using the same procedures as described for the compound **228a**, example 121 (scheme 47, table 1) starting from the thiophenols **225b-f** via the intermediates **226b-f** and **227b-f** (scheme 47).

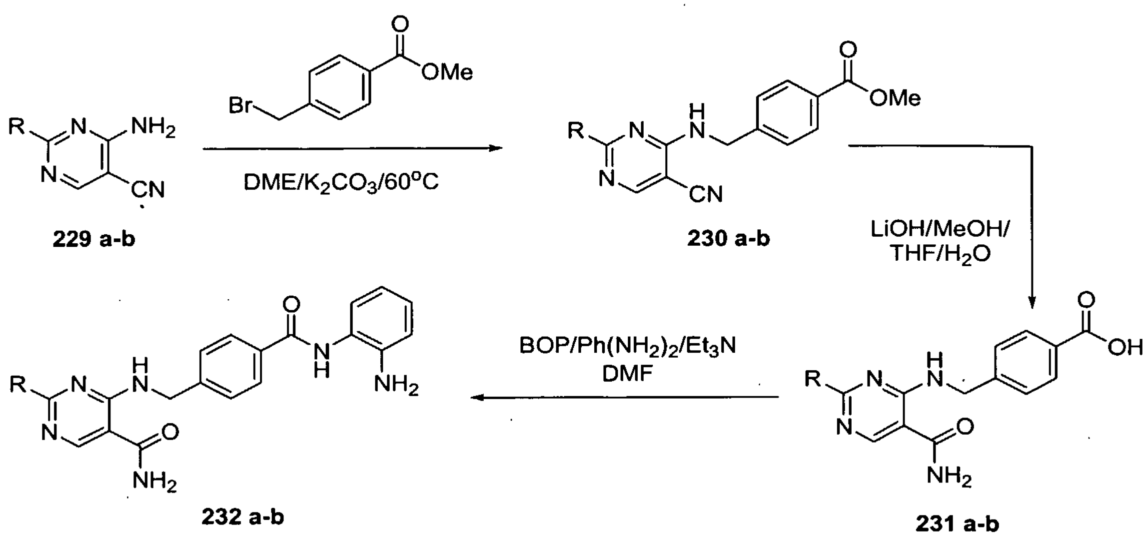
Table 8



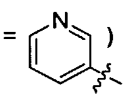
Ex	Cmpd	Ar	R	Name	Characterization	Scheme
121	**228b**		H	N-(2-Amino-phenyl)-4-(4-thiophen-2-yl-pyrimidin-2-ylsulfanylmethyl)-benzamide	**^{1}H NMR: (DMSO-d_6) δ(ppm):** 9.57 (bs, 1H), 8.59 (d, J=5.1 Hz, 1H), 8.07 (dd, J=1.2, 3.9 Hz, 1H), 7.87-7.82 (m, 3H), 7.68 (d, J=5.1 Hz, 1H), 7.59 (d, J=8.2, 2H), 7.24 (dd, J=5.1, 3.5Hz, 1H), 7.10 (d, J=7.0 Hz, 1H), 6.93 (dt, J= 7.8, 1.6 Hz, 1H), 6.73 (dd, J=7.8, 1.2 Hz, 1H), 6.55 (dt, J=7.4, 1.2 Hz, 1H), 4.87 (bs, 2H), 4.51 (s, 2H).	47

Ex	Cmpd	Ar	R	Name	Characterization	Scheme
122	**228c**		Me	N-(2-Amino-phenyl)-4-(4-pyridin-3-yl-pyrimidin-2-ylsulfanylmethyl)-benzamide	**^{1}H NMR: (DMSO-d$_6$) δ(ppm):** 9.65 (bs, 1H), 9.45-9.21 (m, 1H), 8.66-8.60 (m, 2H), 8.41-8.39 (m, 1H), 7.77-7.76 (m, 3H), 7.52-7.41 (m, 3H), 7.05-6.98 (m, 1H), 6.81 (dd, J=6.8, 7.2 Hz, 1H), 6.61 (d, J= 6.9 Hz, 1H), 6.42 (dd, J=7.0, 8.8 Hz, 1H), 4.74 (bs, 2H), 4.46 (s, 2H).	47
123	**228d**		Me	N-(2-Amino-phenyl)-4-{1-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanyl]-ethyl}-benzamide	**^{1}H NMR: (CDCl$_3$) δ(ppm):** 9.58 (bs, 1H), 8.57 (d, J=5.3 Hz, 1H), 8.13 (dd, J=2.1, 6.8 Hz, 2H), 7.91 (d, J=8.0 Hz, 2H), 7.68 (d, J=5.5 Hz, 1H), 7.63 (d, J=8.2, 2H), 7.12 (m, 3H), 6.93 (dt, J=1.4, 7.8 Hz, 1H), 7.40 (dd, J= 1.4, 8.0 Hz, 1H), 6.56 (dt, J=1.3, 7.6 Hz, 1H), 4.87 (s, 2H), 3.83 (s, 3H), 1.76 (d, J=7.0 Hz, 3H).	47
124	**228e**		H	N-(2-Amino-phenyl)-4-(5-pyridin-2-yl-4,5-dihydro-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-benzamide	**^{1}H NMR: (CD$_3$OD) δ(ppm):** 9.60 (bs, 1H), 8.58 (bd, J=4.7 Hz, 1H), 8.24 (s, 1H), 7.90 (d, J=8.1 Hz, 2H), 7.87-7.80 (m, 2H), 7.52 (d, J=8.2Hz, 2H), 7.43-7.39 (m, 1H), 7.11 (d, J=7.2 Hz, 1H), 6.93 (dt, J= 1.6, 8.0 Hz, 1H), 6.74 (dd, J=1.4, 8.0 Hz, 1H), 6.55 (ddd, J=1.6, 6.3, 7.4Hz, 1H), 4.88 (bs, 2H), 4.56 (s, 2H).	47
125	**228f**		H	N-(2-Amino-phenyl)-4-[6-(4-chloro-phenyl)-pyridin-2-ylsulfanylmethyl]-benzamide	**^{1}H NMR: (CD$_3$OD) δ(ppm):** 9.57 (bs, 1H), 8.68 (d, J=5.2 Hz, 1H), 8.20 (bd, J=8.8Hz, 2H), 7.88 (d, J=8.2 Hz, 2H), 7.80 (d , J=5.2 Hz, 1H), 7.62-7.55 (m, 4H), 7.10 (d, J=7.6 Hz, 1H), 6.92 (dt, J=1.6, 8.0 Hz, 1H), 6.72 (dd, J= 1.4, 8.0 Hz, 1H), 6.54 (dt, J=1.2, 7.6 Hz, 1H), 4.86 (bs, 2H), 4.55 (s, 2H).	47

Scheme 48



232 a: Example 126 (R = SMe)

232 b: Example 127 (R = )

Example 126:

4-[4-(2-Amino-phenylcarbamoyl)-benzylamino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid amide (232a)

[0680] Step 1: 4-[(5-Cyano-2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-benzoic acid methyl ester (230a)

[0681] To a solution of 4-amino-2-methylsulfanyl-pyrimidine-5-carbonitrile (**229a**) (200 mg, 1.2 mmol) in DME (10 ml) were added 4-bromomethyl-benzoic acid methyl ester (274 mg, 1.2 mmol) and K_2CO_3 (663 mg, 4.8 mmol) at room temperature. The reaction mixture was heated at 100 °C for 5h, overnight at 60°C, cooled, filtered and concentrated *in vacuo*. The crude product was used in the next reaction without further purification. LRMS: 314.3(calc.); 315.3 (obt.) $(MH)^+$.

[0682] Step 2: 4-[(5-Carbamoyl-2-methylsulfanyl-pyrimidin-4-ylamino)-methyl]-benzoic acid (231a)

[0683] Title compound **231a** was obtained following the procedure described in example 121, step 2 (scheme 47) but substituting compound **226a** for compound **230a** (227 mg, 60% yield). LRMS (calc.): 318.3, (found): 319.3.

[0684] Step 3: 4-[4-(2-Amino-phenylcarbamoyl)-benzylamino]-2-methylsulfanyl-pyrimidine-5-carboxylic acid amide (232a)

[0685] Title compound **232a** was obtained by a coupling reaction of acid **231a** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1) (80%

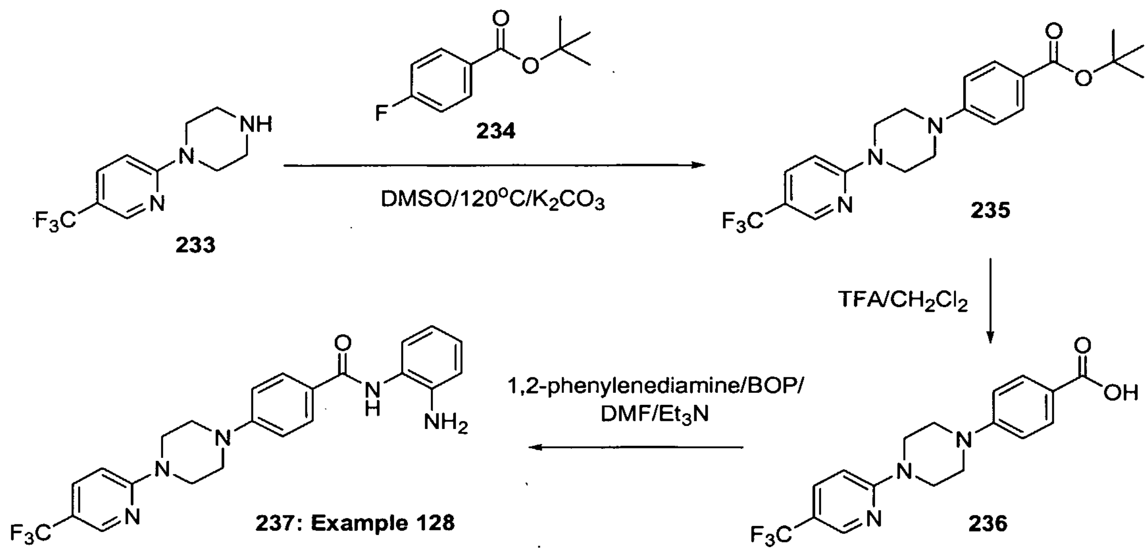
yield). ^{1}H NMR: (DMSO) δ (ppm): 9.39 (bs, 1H), 9.35 (bs, 2H), 8.32 (s, 1H), 7.71 (d, J=8.4 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 6.94 (d, J=7.6 Hz, 1H), 6.75 (dt, J=1.4, 8.2, 1H), 6.56 (dd, J=1.5, 8.0Hz, 1H), 6.39 (t, J=7.4 Hz, 1H), 4.54 (s, 2H), 2.30 (s, 3H). LRMS: (calc.) 408.5; (obt.) 409.5 $(MH)^+$.

Example 127:

4-[4-(2-Amino-phenylcarbamoyl)-benzylamino]-2-pyridin-3-yl-pyrimidine-5-carboxylic acid amide (232b)

[0686] Title compound **232b** was prepared following the same procedures as described for the compound **232a**, example 126 (scheme 48) starting from the aminonitrile **229b** via the intermediates **230b** and **231b**. ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.48 (bs, 3H), 8.86 (s, 1H), 8.74-8.73 (m, 1H), 8.64-8.61 (m, 1H), 8.19 (bs, 1H), 7.98 (d, J=8.8 Hz, 2H), 7.71 (bs, 1H), 7.60-7.57 (m, 3H), 7.18 (d, J=8.4 Hz, 1H), 7.00 (t, J=6.8 Hz, 1H), 6.81 (d, J=8.8 Hz, 1H), 6.63 (t, J=8.0 Hz, 1H), 4.95 (d, J=6.8 Hz, 2H).

Scheme 49



Example 128:

***N*-(2-aminophenyl)-4-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)benzamide (237)**

[0687] Step 1: 4-[4-(4-Trifluoromethyl- pyridin-2-yl)-piperazin-1-yl]-benzoic acid tert-butyl ester (235)

[0688] To a solution of 1-(4-trifluoromethyl- pyridin-2-yl)-piperazine (**233**) (500mg, 2.16 mmol) in DMSO were added 4-fluoro-benzoic acid tert-butyl ester (466 mg, 2.37 mmol) (**234**) and K_2CO_3 (1.2 g, 11.3 mmol). The mixture was heated for 16 h at 130°C, cooled, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (eluent AcOEt-hexane

from 40:60 to pure AcOEt) to afford the title compound **244** (162 mg, 18 % yield). LRMS: (calcd.) 406.4: (found) 407.4 $(MH)^+$.

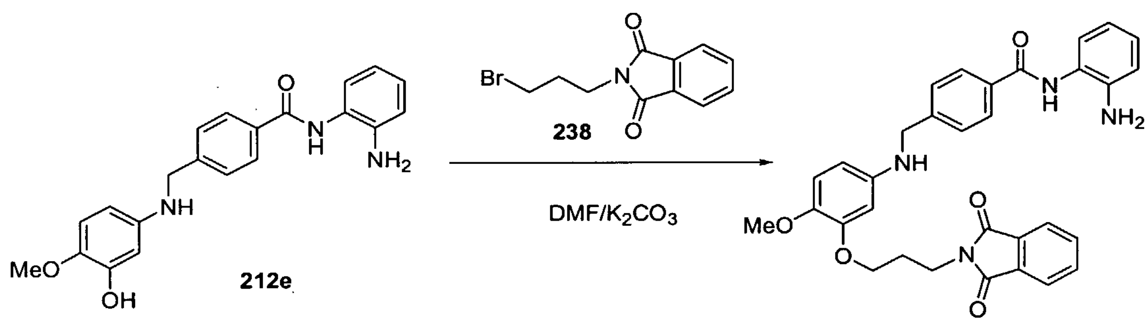
[0689] Step 2: 4-[4-(4-Trifluoromethyl- pyridin-2-yl)-piperazin-1-yl]-benzoic acid (236)

[0690] The title compound **236** was obtained starting from the compound **235** following the procedure described in the scheme 28, step 5 (example 68) (99% yield). LRMS 350.3 (calcd.), 351.3 (found).

[0691] Step 3: N-(2-Amino-phenyl)-4-[4-(4-trifluoromethyl- pyridin-2-yl)-piperazin-1-yl]-benzamide (237)

[0692] The title compound **237** was obtained by coupling acid **236** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1) (96% yield). ^{1}H NMR: (DMSO) δ (ppm): 9.43 (bs, 1H), 8.43 (s, 1H), 7.93 (bs, 2H), 7.88 (d, J=8.8 Hz, 2H), 7.81 (dd, J=2.4, 8.8 Hz, 1H), 7.13 (d, J=8.0 Hz, 1H), 7.04-7.00 (m, 3H), 6.96 (t, J=7.6 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 6.58 (t, J=7.6 Hz, 1H), 4.84 (bs, 2H), 3.82-3.79(m, 4H), 3.44-3.40 (m, 4H). LRMS: (calcd.) 440.4; (found.) 441.4 $(MH)^+$.

Scheme 50



239: Example 129

Example 129:

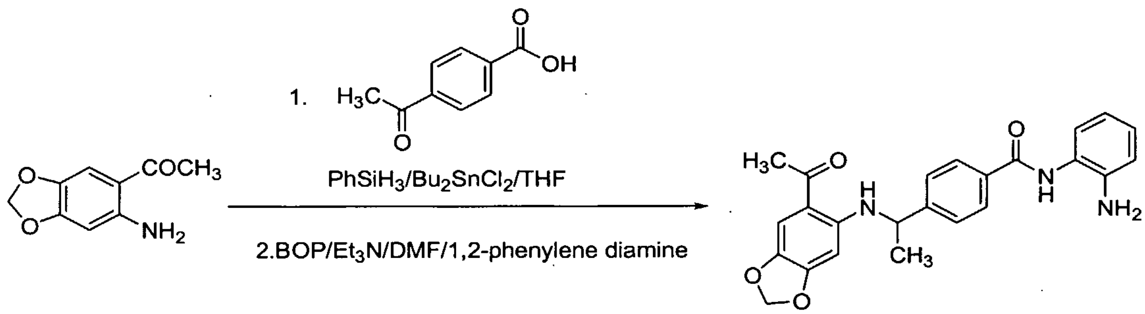
N-(2-Amino-phenyl)-4-({3-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propoxy]-4-methoxy-phenylamino}-methyl)-benzamide (239)

[0693] Step 1: N-(2-Amino-phenyl)-4-({3-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propoxy]-4-methoxy-phenylamino}-methyl)-benzamide (239)

[0694] To a solution of N-(2-amino-phenyl)-4-[(3-hydroxy-4-methoxy-phenylamino)-methyl]-benzamide (**212e**) (586 mg, 0.66 mmol) in DMF (10 ml) were added 2-(3-bromo-propyl)-isoindole-1,3-dione (**238**) (176 mg, 0.66 mmol) and K_2CO_3 (365 mg, 2.64 mmol) at room temperature. The reaction mixture was heated at 100°C for 1h then overnight at 60°C, cooled, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (eluent from AcOEt-

hexane (40:60) to pure AcOEt) to afford **239** (168 mg, 46 % yield). ^{1}H NMR: (DMSO) δ (ppm): 9.57 (bs, 1H), 7.88 (d, J=8.0 Hz, 2H), 7.84-7.75 (m, 4H), 7.44 (d, J= 8.0 Hz, 2H), 7.12 (d, J=7.2 Hz, 1H), 6.92 (t, J=8.8 Hz, 1H), 6.75 (dd, J=1.2, 7.6 Hz, 1H), 6.57 (d, J=8.4 Hz, 2H), 6.27 (d, J=2.4 Hz, 1H), 6.00-5.93 (m, 2H), 4.87 (s, 2H), 4.27 (d, J=6.0Hz, 2H), 3.89 (dd, J=5.6, 6.0 Hz, 2H), 3.74 (dd, J=6.4, 6.8 Hz, 2H), 3.42 (s, 3H), 2.06-2.01 (m, 2H). LRMS: (calcd.) 550.4; (found.) 551.5(MH)$^+$.

Scheme 51



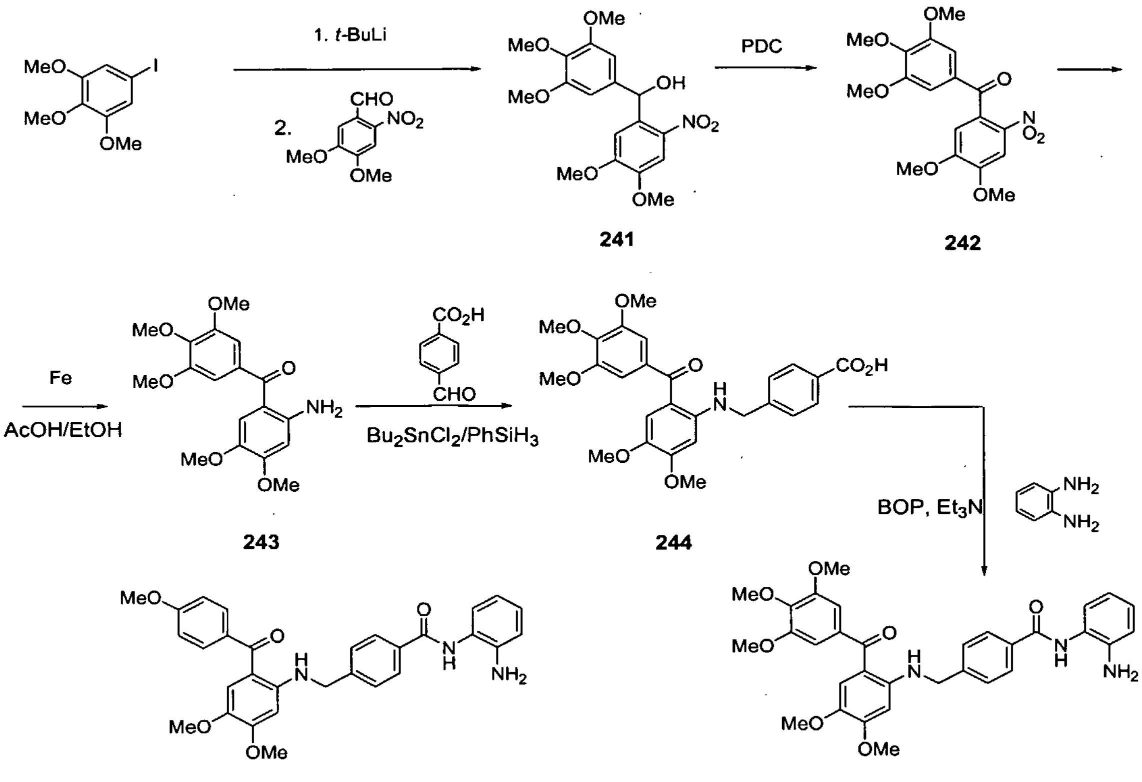
240: Example 130

__Example 130:__

4-[1-(6-Acetyl-benzo[1,3]dioxol-5-ylamino)-ethyl]-N-(2-amino-phenyl)-benzamide (240)

[0695] Title compound **240** was prepared using the same procedures as described for the compound **212a**, example 99 (scheme 42, table 1), starting from 1-(6-amino-benzo[1,3]dioxol-5-yl)-ethanone and 4-acetylbenzoic acid (scheme 51). ^{1}H NMR: (DMSO-d$_6$) δ(ppm): 8.69 (s, 1H), 7.03 (d, J=7.8 Hz, 2H), 6.64 (d, J=7.8 Hz, 2H), 6.29 (dd, J= 8.3, 7.8 Hz, 1H), 6.09 (t, J=7.8, 7.3 Hz, 1H), 5.90 (d, J=7.8, 1H), 5.72 (d, J=6.8 Hz, 1H), 5.70 (s, 1H), 5.16 (d, J=8.8 Hz, 1H), 4.88 (s, 1H), 4.84 (s, 1H), 4.07 (bd, 1H), 2.30 (s, 3H), 0.62 (d, J=6.83, 3H).

Scheme 52



246: Example 132

245: Example 131

Example 131

N-(2-Amino-phenyl)-4-{[4,5-dimethoxy-2-(3,4,5-trimethoxy-benzoyl)-phenylamino]-methyl}-benzamide (245)

[0696] Step 1: (4,5-Dimethoxy-2-nitro-phenyl)-(3,4,5-trimethoxy-phenyl)-methanol (241):

[0697] A flame-dried round-bottomed flask under N_2 atmosphere was charged with 5-iodo-1,2,3-trimethoxybenzene (2.92g, 9.93 mmol) and THF (31mL) was added. The solution was cooled down to -78°C and 1.5 M solution of *t*-BuLi in pentane (13.6mL, 20.57 mmol) was added dropwise. The mixture was stirred for 1h and transferred *via canula* to a precooled (-78°C) solution of 6-nitroveratraldehyde (2.02g, 9.57 mmol) in THF (12mL) under N_2 atmosphere. The resulting mixture was stirred for 2 h and slowly warmed up to 0°C, quenched with saturated aqueous solution of NH_4Cl and allowed to warm-up to rt. Solvent was removed *in vacuo* and the residue was partitioned between water and DCM. Organic layer was collected and washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography using EtOAc/DCM (9:91) affording the title compound **241** (1.46g, 40% yield) ^1H NMR ($CDCl_3$) δ (ppm): 7.61 (s, 1H), 7.16 (s, 1H), 6.58 (s, 2H), 6.45 (s, 1H), 6.09 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.83 (s, 6H). m/z: 402.4 (MH^+).

[0698] <u>Step 2: (4,5-Dimethoxy-2-nitro-phenyl)-(3,4,5-trimethoxy-phenyl)-methanone (242):</u>

[0699] Powdered 4Å molecular sieves (583 mg) and pyridinium dichromate (2.17g, 5.77 mmol) were successively added to a stirred solution of intermediate **241** (1.46g, 3.84 mmol) in of anhydrous DCM (38.5mL) at 0°C. The mixture was stirred at rt for 15 h. More PDC (290mg, 0.770 mmol) was added and the mixture was stirred for another 4h, The diluted with ether and filtered through a celite pad. The filtrate was concentrated and the brown solid was purified by flash chromatography using EtOAc/DCM (7:93) affording the title compound **242** (551mg, 41%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (s, 1H), 6.99 (s, 2H), 6.86 (s, 1H), 4.06 (s, 3H), 4.00 (s, 3H), 3.93 (s, 3H), 3.84 (s, 6H). m/z: 378.4 (MH^+).

[0700] <u>Step 3: (2-Amino-4,5-dimethoxy-phenyl)-(3,4,5-trimethoxy-phenyl)-methanone (243):</u>

[0701] Iron powder (653 mg, 11.7 mmol) was added to a suspension of intermediate **199** (552mg, 1.46 mmol) in a mixture of EtOH (5.11mL), H_2O (2.56 mL) and AcOH (5.11 mL) and 2 drops of concentrated HCl were added to the solution. The mixture was vigorously stirred while refluxing for 1h, cooled down to rt and filtered through a celite pad. The filtrate was concentrated *in vacuo* and the aqueous residue partitioned between DCM and H_2O. The organic layer was washed with sat. $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo* affording the title compound **243** (393mg, 77%). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.00 (s, 1H), 6.88 (s, 2H), 6.23 (s, 1H), 3.92 (m, 6H), 3.88 (s, 6H), 3.70 (s, 3H). m/z: 348.4 (MH^+).

[0702] <u>Step 4: 4-{[4,5-Dimethoxy-2-(3,4,5-trimethoxy-benzoyl)-phenylamino]-methyl}-benzoic acid (244):</u>

[0703] The title compound **244** was obtained following same procedure as for the reductive amination described in scheme 3, step 2 (example 12) starting from compound **243** (46% yield). m/z: 482.5 (MH^+).

[0704] <u>Step 5: N-(2-Amino-phenyl)-4-{[4,5-dimethoxy-2-(3,4,5-trimethoxy-benzoyl)-phenylamino]-methyl}-benzamide (245)</u>

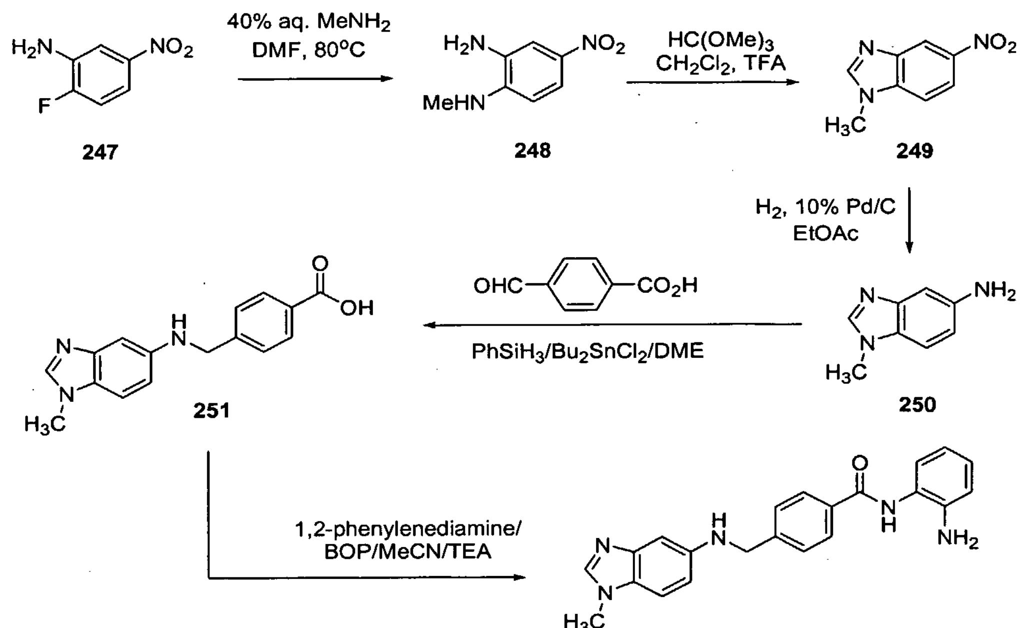
[0705] The title compound **245** was obtained following the same procedure as for the BOP coupling described in scheme 1, step 5 (example 1) using compound **244** as starting material. (38% yield). ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.61 (s, 1H), 9.24 (t, J= 5.7 Hz, 1H), 7.95 (d, J= 8.2 Hz, 2H), 7.51 (d, J= 8.2 Hz, 2H) 7.13 (d, J= 8.0 Hz, 1H), 6.98 (s, 1H), 6.94 (td, J= 7.6, 1.2 Hz, 1H) 6.84 (s, 2H), 6.75 (dd, J= 8.0, 1.3 Hz, 1H), 6.57 (t, J= 7.2 Hz, 1H), 6.35 (s, 1H), 4.89 (s, 2H), 4.62 (d, J= 5.7 Hz, 2H), 3.79 (s, 6H), 3.76 (s, 3H), 3.73 (s, 3H), 3.54 (s, 3H). m/z: 572.5 (MH^+).

<u>Example 132</u>

N-(2-Amino-phenyl)-4-{[4,5-dimethoxy-2-(4-methoxy-benzoyl)-phenylamino]-methyl}-benzamide (246)

[0706] The title compound **246** was obtained following the same procedures described in example 131 but substituting the organolithium reagent obtained from 5-iodo-1,2,3-trimethoxybenzene and *t*-BuLi for the commercially available Grignard reagent 4-methoxyphenyl magnesium bromide (8.4% overall yield). ^{1}H NMR: (DMSO-d$_6$) δ(ppm): 9.62 (s, 1H), 9.10 (t, J= 5.7 Hz, 1H), 7.95 (d, J= 8.2, 2H), 7.57 (d, J= 8.8 Hz, 2H), 7.52 (d, J= 8.2 Hz, 2H), 7.14 (d, J= 6.6 Hz, 1H), 7.04 (d, J= 8.8 Hz, 2H), 6.95 (td, J= 8.2, 1.6 Hz, 2H), 6.94 (s, 1H), 6.76 (dd, J= 7.8, 1.4 Hz, 1H), 6.58 (t, J= 6.5 Hz, 2H), 6.35 (s, 2H), 4.90 (s, 2H), 4.62 (d, J= 5.3 Hz, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.54 (s, 3H). m/z: 512.6 (MH$^+$).

Scheme 53



Example 133

N-(2-Amino-phenyl)-4-[(1-methyl-1H-benzoimidazol-5-ylamino)-methyl]-benzamide (252)

[0707] Step 1. N1-Methyl-4-nitro-benzene-1,2-diamine (248):

[0708] A solution of fluoride **247** (5.41g, 34.7 mmol) in DMF (40mL) was treated with 40%w/w solution of MeNH$_2$ in water (10mL, 128 mmol). The mixture stirred at 90 □C for 3h, diluted with EtOAc, washed with saturated aqueous NaHCO$_3$. Organic phase was dried over MgSO$_4$, evaporated and the residue was purified by flash chromatography (eluent 50% EtOAc in CH$_2$Cl$_2$) to afford compound **248** (5.31g, 92% yield). ^{1}H NMR: (CDCl$_3$) δ (ppm): 7.75 (dd, J = 2.6,

8.8 Hz, 1H), 7.53 (d, J = 2.6 Hz, 1H), 6.45 (d, J = 8.8 Hz, 1H), 4.24 (bs, 3H), 2.91 (s, 3H). LRMS: (calcd.) 167.2; (found) 168.1 $(MH)^+$.

[0709] Step 2. 1-Methyl-5-nitro-1H-benzoimidazole (249)

[0710] To a suspension of diamine **248** (1.14g, 6.80mmol) in CH_2Cl_2 (10mL) was added trimethyl orthoformate (5 mL, 46 mmol, 6.7 eq) (or any other acylating agent of choice, 6 eq) followed by TFA (0.43 mL, 5.6 mmol, 0.8 eq) and the mixture was stirred at room temperature for 2h. Precipitate was collected by filtration, washed with CH_2Cl_2 and dried to afford the title compound **249** as TFA salt (1.23g, 62% yield). ^{1}H NMR: ($CDCl_3$) δ (ppm): 8.57 (d, J = 1.8 Hz, 1H), 8.20 (dd, J = 1.8, 9.2 Hz, 1H), 8.18 (s, 1H), 7.54 (d, J = 9.2 Hz, 1H), 3.94 (s, 3H). LRMS: (calc.) 177.2; (obt.) 178.1 $(MH)^+$.

[0711] Step 3. 1-Methyl-1H-benzoimidazol-5-ylamine (250)

[0712] Title compound **250** was obtained by catalytic hydrogenation of nitro compound **249** following the procedure described in the scheme 25, step 2 (example 64). LRMS: (calc.) 147.2; (obt.) 148.1 $(MH)^+$.

[0713] Step 4: 4-[(1-Methyl-1H-benzoimidazol-5-ylamino)-methyl]-benzoic acid (251)

[0714] Title compound **251** was obtained by reacting the amine **250** with 4-formyl-benzoic acid, following the procedure described in the scheme 3, step 2 (example 12). ^{1}H NMR, (DMSO) δ (ppm): 8.24 (s, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 8.9 Hz, 1H), 6.80 (d, J = 8.9 Hz, 1H), 6.61 (s, 1H), 4.39 (s, 2H), 3.77 (s, 3H). LRMS: (calc.) 281.3; (obt.) 282.3 $(MH)^+$.

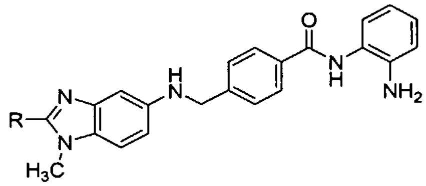
[0715] Step 5: N-(2-Amino-phenyl)-4-[(1-methyl-1H-benzoimidazol-5-ylamino)-methyl]-benzamide (255)

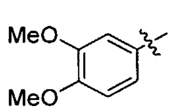
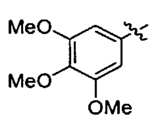
[0716] Title compound **252** was obtained by coupling of acid **251** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1). ^{1}H NMR: (DMSO) δ (ppm): 9.57 (s, 1H), 8.00 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.76 (m, 2H), 6.62 (s, 1H), 6.57 (d, J = 7.5 Hz, 1H), 6.17 (bs, 1H), 5.01 (bs, 2H), 4.40 (s, 2H), 3.73 (s, 3H).LRMS: (calc.) 371.4; (obt.) 372.4 $(MH)^+$.

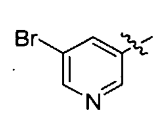
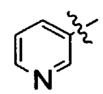
Examples 134-140

[0717] Examples 134-140 (compounds **253-259**) were prepared similarly to the example 134 (compound **252**) according to the scheme 53 substituting trimethyl orthoformate by corresponding acyl chlorides.

Table 9. Characterization of compounds prepared as example 133 (scheme 53)



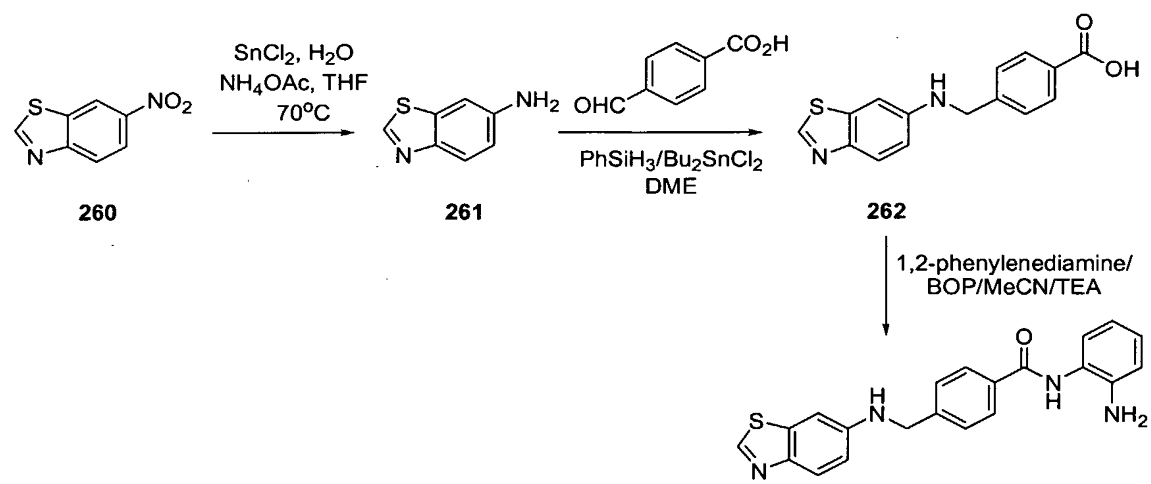
Ex.	Cmpd	R	Name	Characterization	Scheme
134	**252**	Me	N-(2-Amino-phenyl)-4-[(1,2-dimethyl-1H-benzoimidazol-5-ylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.50 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.74 (m, 2H), 6.59 (m, 2H), 6.30 (bs, 1H), 5.00 (bs, 2H), 4.40 (s, 2H), 3.68 (s, 3H), 2.49 (s, 3H). **LRMS**: (calc.) 385.5; (obt.) 386.4 $(MH)^+$.	**53**
135	**254**	$MeOCH_2$	N-(2-Amino-phenyl)-4-[(2-methoxy-methyl-1-methyl-1H-benzoimidazol-5-ylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.57 (s, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.73 (m, 2H), 6.59 (m, 2H), 6.14 (bs, 1H), 4.96 (bs, 2H), 4.57 (bs, 2H), 4.38 (s, 2H), 3.68 (s, 3H), 3.27 (s, 3H). **LRMS**: (calc.) 415.5; (obt.) 416.5 $(MH)^+$.	**53**
136	**255**	CF_3	N-(2-Amino-phenyl)-4-[(1-methyl-2-trifluoromethyl-1H-benzoimidazol-5-ylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.57 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2, 2H), 7.46 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 6.6 Hz, 1H), 6.96-6.92 (m, 2H), 6.75 (dd, J = 1.6, 8.2 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 6.56 (ddd, J = 1.6, 7.4, 7.8 Hz, 1H), 6.45 (t, J = 6.2 Hz, 1H), 4.88 (bs, 2H), 4.40 (d, J = 5.9 Hz, 2H), 3.85 (d, J = 0.8 Hz, 3H), **LRMS**: (calc.) 339.4; (obt.) 440.5 $(MH)^+$.	**53**
137	**256**		N-(2-Amino-phenyl)-4-{[2-(3,4-dimethoxy-phenyl)-1-methyl-1H-benzoimidazol-5-ylamino]-methyl}-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.58 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.32-7.27 (m, 3H), 7.14 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.95 (t, J=7.5, 1H), 6.77-6.73 (m, 2H), 6.62 (s, 1H), 6.58 (t, J=8.0, 1H), 6.16 (bs, 1H), 4.87 (bs, 2H), 4.40 (d, J=4.5, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H). **LRMS**: (calc.) 507.6; (obt.) 508.4 $(MH)^+$.	**53**
138	**257**		N-(2-Amino-phenyl)-4-{[1-methyl-2-(3,4,5-trimethoxy-phenyl)-1H-benzoimidazol-5-ylamino]-methyl}-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.58 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.03 (s, 2H), 6.95 (t, J=8.0, 1H), 6.77 (m, 2H), 6.62 (s, 1H), 6.58 (t, J=7.0, 1H), 6.27 (bs, 1H), 4.41 (bs, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.73 (s, 3H). **LRMS**: (calc.) 537.6; (obt.) 538.5 $(MH)^+$.	**53**

Ex.	Cmpd	R	Name	Characterization	Scheme
139	258		N-(2-Amino-phenyl)-4-{[2-(5-bromo-pyridin-3-yl)-1-methyl-1H-benzoimidazol-5-ylamino]-methyl}-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.58 (s, 1H), 8.97 (s, 1H), 8.82 (s, 1H), 8.44 (s, 1H), 7.92 (d, J = 7.0 Hz, 2H), 7.52 (d, J = 7.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 6.95 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.64 (s, 1H), 6.57 (m, 1H), 6.27 (s, 1H), 4.87 (bs, 2H), 4.41 (d, J=5.5, 2H), 3.83 (s, 3H) **LRMS**: (calc.) 527.4; (obt.) 528.3 $(MH)^+$.	53
140	259		N-(2-Amino-phenyl)-4-[(1-methyl-2-pyridin-3-yl-1H-benzoimidazol-5-ylamino)-methyl]-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.57 (s, 1H), 8.98 (s, 1H), 8.69 (s, 1H), 8.20 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.57 (m, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 9.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 8.0 Hz, 2H), 6.66 (s, 1H), 6.58 (t, J=7.5, 1H), 6.27 (bs, 1H), 4.90 (bs, 2H), 4.42 (bs, 2H), 3.81 (s, 3H) **LRMS**: (calc.) 448.52; (obt.) 449.2 $(MH)^+$.	53

Example 141

N-(2-Amino-phenyl)-4-(benzothiazol-6-ylaminomethyl)-benzamide (263)

Scheme 54



260 **261** **262**

263: Example 141

[0718] Step 1. Benzothiazol-6-ylamine (261)

[0719] Title compound **261** was obtained by reducing the nitro compound **260** with tin(II) chloride following the procedure described in the scheme 33, compound **143** (example 79). LRMS: (calc.) 150.2; (obt.) 151.1 $(MH)^+$.

[0720] Step 2: 4-(Benzothiazol-6-ylaminomethyl)-benzoic acid (262)

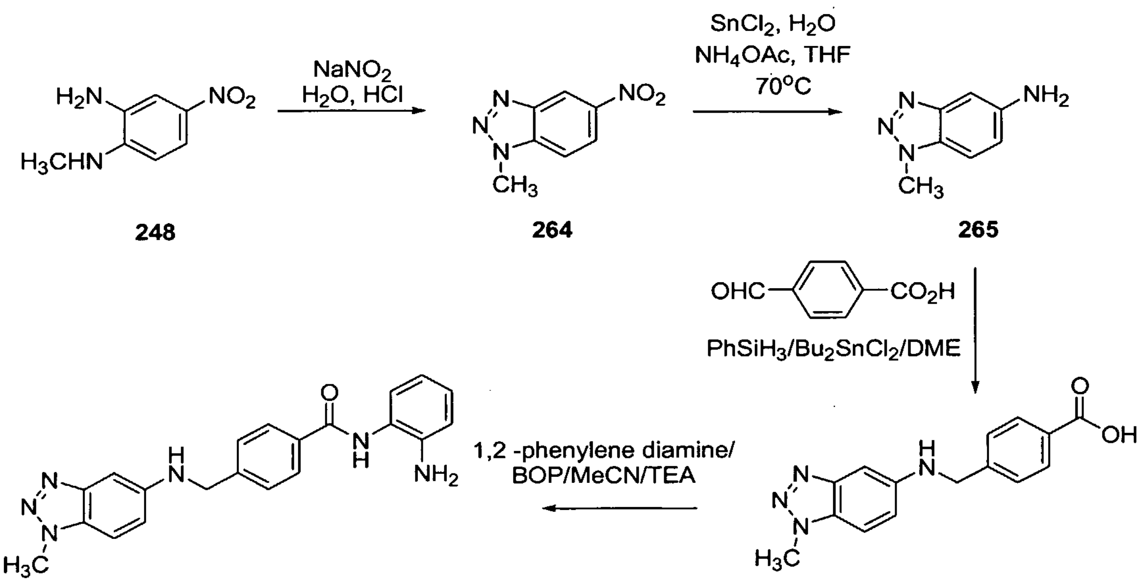
[0721] Title compound **262** was obtained by reacting amine **261** with 4-formyl-benzoic acid, following the procedure described in the scheme 3, step 2 (example 12). ^{1}H NMR, (DMSO) δ

(ppm): 8.04 (s, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 1.8 Hz, 1H), 6.89 (dd, J = 1.8, 8.1 Hz, 1H), 4.42 (s, 2H). LRMS: (calc.) 284.3; (obt.) 285.2 $(MH)^+$.

[0722] Step 3: -(2-Amino-phenyl)-4-(benzothiazol-6-ylaminomethyl)-benzamide (263)

[0723] Title compound **263** was obtained by coupling of acid **262** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1). ^{1}H NMR: (DMSO) δ (ppm): 9.59 (s, 1H), 8.89 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.5 Hz, 1H), 7.08 (s, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.76 (m, 2H), 6.58 (s, 1H), 4.87 (bs, 2H), 4.43 (bs, 2H). LRMS: (calc.) 374.5; (obt.) 375.4 $(MH)^+$.

Scheme 55



Example 142

N-(2-Amino-phenyl)-4-[(1-methyl-1H-benzotriazol-5-ylamino)-methyl]-benzamide (267)

[0724] Step 1: 1-Methyl-5-nitro-1H-benzotriazole (264)

[0725] A stirred suspension of diamine **248** (1.13g, 6.76mmol) and concentrated HCl (5.6 mL, 67 mmol) in water (22 mL) at 0□C, was treated with a solution of $NaNO_2$ (586 mg, 8.5 mmol) in water (10 mL). The mixture was stirred at the same conditions for 3h, warmed to room temperature, neutralized with a 5% w/v solution of KOH in water and filtered. The solid was washed with cold water and dried to afford title compound **264** (975mg, 81% yield). ^{1}H NMR: (DMSO) δ (ppm): 9.00 (d, J = 1.3 Hz, 1H), 8.39 (dd, J = 1.3, 8.8 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 4.40 (s, 3H).

[0726] Step 2: 1-Methyl-1H-benzotriazol-5-ylamine (265).

[0727] Title compound **265** was obtained by reduction of the nitro compound **264** with tin(II) chloride, following the same procedure described in the scheme 33, compound **143** (example 79). ^{1}H NMR: (CD_3OD) δ (ppm): 7.32 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 1.7 Hz, 1H), 6.99 (dd, J = 1.7, 8.8 Hz, 1H), 4.21 (s, 3H). LRMS: (calc.) 148.3; (obt.) 149.3 $(MH)^+$.

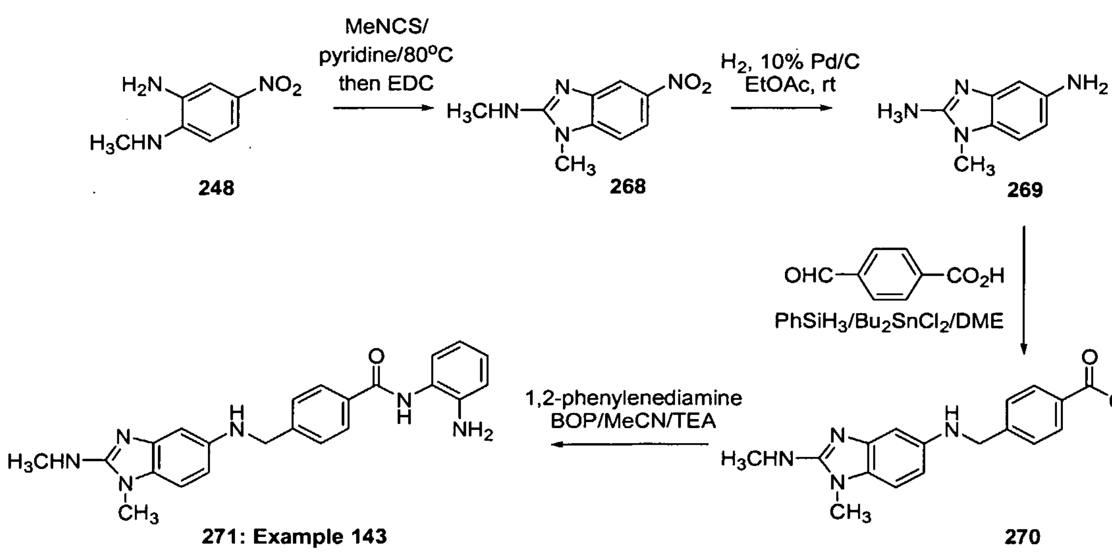
[0728] Step 3: 4-[(1-Methyl-1H-benzotriazol-5-ylamino)-methyl]-benzoic acid (266).

[0729] Title compound **266** was obtained by reacting amine **265** with 4-formyl-benzoic acid, following the procedure described in the scheme 3, step 2 (example 12). LRMS: (calc.) 282.3; (obt.) 283.3 $(MH)^+$.

[0730] Step 4: N-(2-Amino-phenyl)-4-[(1-methyl-1H-benzotriazol-5-ylamino)-methyl]-benzamide (267)

[0731] Title compound **267** was obtained by coupling of acid **266** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1). ^{1}H NMR: (DMSO) δ (ppm): 9.58 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.53 (m, 3H), 7.14 (d, J = 8.0 Hz, 1H), 7.07 (dd, J = 2.0, 8.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 6.61 (s, 2H), 4.87 (bs, 2H), 4.42 (d, J = 6.0 Hz, 2H), 4.16 (s, 3H). LRMS: (calc.) 372.4; (obt.) 373.5 $(MH)^+$.

Scheme 56



Example 143

N-(2-Amino-phenyl)-4-[(1-methyl-2-methylamino-1H-benzoimidazol-5-ylamino)-methyl]-benzamide (271)

[0732] Step 1: Methyl-(1-methyl-5-nitro-1H-benzoimidazol-2-yl)-amine (268)

[0733] A solution of diamine **248** (1.88g, 11.2 mmol) in pyridine (20 mL) was treated with methyl isothiocyanate (970 mg, 12.9 mmol) and the mixture was stirred at 80□C for 30 minutes, cooled down to 15 □C, treated with solid EDC (3.03g, 15.8 mmol, 1.40 eq) and the heating continued at 80 □C for 16h. After removal of pyridine *in vacuo*, the residue was purified by flash chromatography (eluent 5% MeOH in CH_2Cl_2) to afford the title compound **268** (1.44g, 62% yield). ^{1}H NMR: (CD_3OD) δ (ppm): 8.12 (d, J = 2.2 Hz, 1H), 7.94 (dd, J = 2.2, 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 4.44 (bs, 2H), 3.51 (s, 3H), 3.04 (s, 3H). LRMS: (calc.) 206.2; (obt.) 207.1 $(MH)^+$.

[0734] Step 2: Methyl-(1-methyl-5-amino-1H-benzoimidazol-2-yl)-amine (269)

[0735] Title compound **269** was obtained by catalytic hydrogenation of the nitro compound **268**, following the procedure described in the scheme 25, step 2 (example 64). ^{1}H NMR: ($CDCl_3$) δ (ppm): 6.70 (s, 1H), 6.62 (d, J = 7.9 Hz, 1H), 6.29 (d, J = 7.9 Hz, 1H), 5.97 (bs, 1H), 3.63 (bs, 2H), 3.15 (s, 3H), 2.90 (s, 3H). LRMS: (calc.) 176.2; (obt.) 177.3 $(MH)^+$.

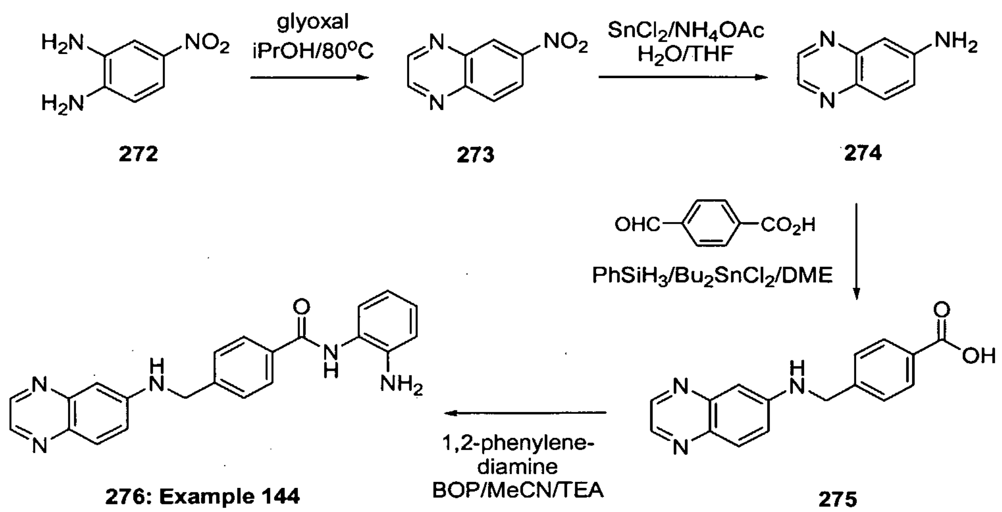
[0736] Step 3: 4-[(1-Methyl-2-methylamino-1H-benzoimidazol-5-ylamino)-methyl]-benzoic acid (270)

[0737] Title compound **270** was obtained by reacting the amine **269** with 4-formyl-benzoic acid with, following the procedure described in the scheme 3, step 2 (example 12).^{1}H NMR: (DMSO) δ (ppm): 8.03 (bs, 1H), 7.88 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 8.3 Hz, 1H), 6.44 (s, 1H), 4.35 (bs, 2H), 3.43 (s, 3H), 2.90 (d, J = 3.5 Hz, 3H). LRMS: (calc.) 310.3; (obt.) 311.4 $(MH)^+$.

[0738] Step 4: N-(2-Amino-phenyl)-4-[(1-methyl-2-methylamino-1H-benzoimidazol-5-ylamino)-methyl]-benzamide (271)

[0739] Title compound **271** was obtained by coupling of the acid **270** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1). ^{1}H NMR: (DMSO) δ (ppm): 9.56 (s, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.39 (s, 1H), 6.31 (m, 2H), 5.75 (t, J = 5.7 Hz, 1H), 4.87 (s, 2H), 4.32 (d, J = 5.7 Hz, 2H), 3.34 (s, 3H), 2.82 (d, J = 4.4 Hz, 3H). LRMS: (calc.) 400.5; (obt.) 401.5 $(MH)^+$

Scheme 57



Example 144

N-(2-Amino-phenyl)-4-(quinoxalin-6-ylaminomethyl)-benzamide (276)

[0740] Step 1: 6-Nitro-quinoxaline (273)

[0741] A solution of nitroaniline **272** (1.04g, 6.76 mmol) in 2-propanol (35 mL) was treated with 40% aqueous glyoxal (0.85 mL, 7.4mmol, 1.1 eq.) (or any other 1,2-dicarbonyl compound, 1.1 eq). The mixture was stirred at 80 ▯C for 2h and concentrated *in vacuo* to afford the title compound **273**, which was used for the next step without further purification. LRMS: (calc.) 175.1; (obt.) 176.1 $(MH)^+$.

[0742] Step 2: Quinoxalin-6-ylamine (274)

[0743] Title compound **274** was obtained by reduction of the nitro compound **273** with tin(II) chloride following the same procedure described in the scheme 33, compound **143** (example 79). LRMS: (calc.) 145.2; (obt.) 146.2 $(MH)^+$.

[0744] Step 3: 4-(Quinoxalin-6-ylaminomethyl)-benzoic acid (275)

[0745] Title compound **275** was obtained by reacting the amine **274** with 4-formyl-benzoic acid, following the procedures described in the scheme 3, step 2 (example 12). LRMS: (calc.) 279.3; (obt.) 280.2 $(MH)^+$.

[0746] Step 4: N-(2-Amino-phenyl)-4-(quinoxalin-6-ylaminomethyl)-benzamide (276)

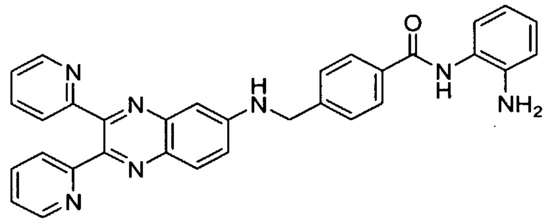
[0747] Title compound **276** was obtained by coupling of acid **275** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1). ^1H NMR: (DMSO) δ (ppm): 9.61 (s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.43 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.40-7.36 (m, 2H), 7.13 (dd, J = 1.6, 6.8 Hz, 1H), 6.95 (dt, J = 1.6, 8.0 Hz, 1H), 6.76 (dd, J = 1.2, 7.8 Hz, 1H), 6.67 (d, J = 2.5 Hz, 1H), 6.59 (dd,

J = 1.2, 7.8 Hz, 1H), 5.05 (bs, 2H), 4.53 (d, J = 5.7 Hz, 2H). LRMS: (calc.) 369.4; (obt.) 370.4 $(MH)^+$.

Example 145

N-(2-Amino-phenyl)-4-[(2,3-di-pyridin-2-yl-quinoxalin-6-ylamino)-methyl]-benzamide (277)

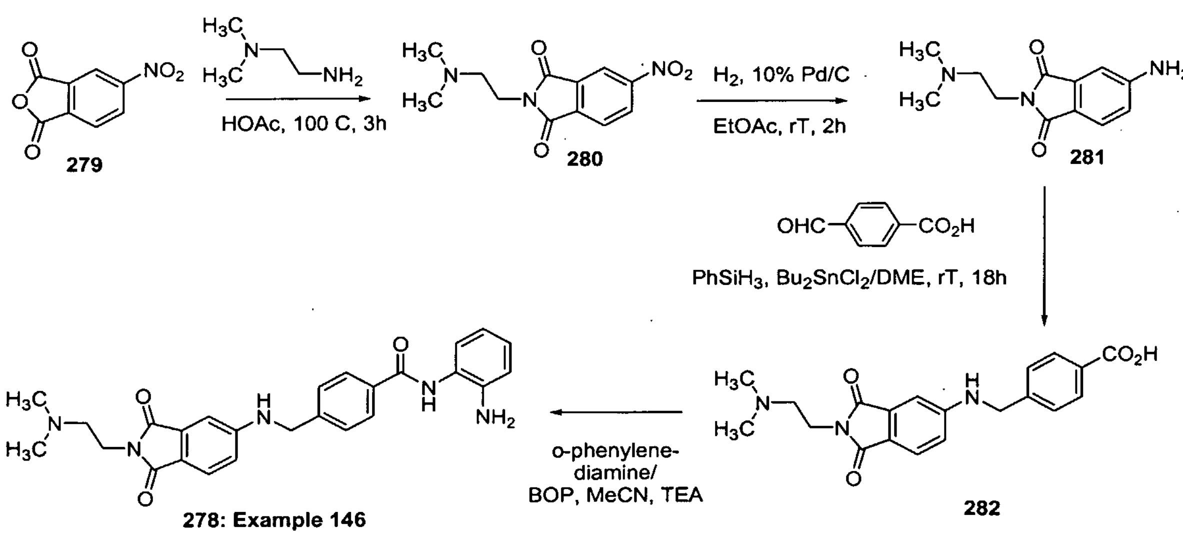
[0748] Title compound was prepared following the procedures depicted in scheme 57 for example 144 using in the first step 1,2-di-pyridin-2-yl-ethane-1,2-dione instead of glyoxal.



277: Example 145

^{1}H NMR: (DMSO) δ (ppm): 9.57 (s, 1H), 8.21 (m, 1H), 8.17 (m, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.89-7.84 (m, 3H), 7.80 (dt, J = 1.8, 7.6 Hz, 1H), 7.55 (m, 3H), 7.46 (dd, J = 2.3, 9.0 Hz, 1H), 7.29-7.22 (m, 2H), 7.12 (d, J = 7.6 Hz, 1H), 6.92 (m, 1H), 6.78 (d, J = 2.3 Hz, 1H),), 6.75 (dd, J = 1.4, 8.3 Hz, 1H), 6.56 (t, J = 7.6 Hz, 1H), 4.87 (bs, 2H), 4.58 (d, J = 6.1 Hz, 2H), 4.34 (d, J = 4.3 Hz, 1H). LRMS: (calc.) 523.6; (obt.) 524.5 $(MH)^+$.

Scheme 58



278: Example 146

Example 146

4-((2-(2-(dimethylamino)ethyl)-1,3-dioxoisoindolin-6-ylamino)methyl)-N-(2-aminophenyl) benzamide (278)

[0749] Step 1. 2-(2-(dimethylamino)ethyl)-5-nitroisoindoline-1,3-dione (280)

[0750] A solution of nitroftalic anhydride **(279)** (995 mg; 5.2 mmol) in acetic acid (12 mL) was treated with neat *N1,N1*-dimethylethane-1,2-diamine (0.75 mL; 5.8 mmol; 1.13 eq.) (or the corresponding amine, 1.3 eq.). The reaction mixture was stirred for 3h at 100°C, cooled down to room temperature, concentrated *in vacuo*; the residue was dissolved in ethyl acetate (250 mL) and washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated, to yield compound **280** as a yellow solid (1.19g; 4.5 mmol; 87%). LRMS: 263.3 (calc.); 264.2 (obt.) $(MH)^+$.

[0751] Step 2. 5-amino-2-(2-(dimethylamino)ethyl)isoindoline-1,3-dione (281)

[0752] Title compound **281** was obtained by catalytic hydrogenation of the nitro compound **280** following the procedure described in the scheme 25, step 2 (example 64). LRMS: 233.3 (calc.); 234.2 (obt.) $(MH)^+$.

[0753] Step 3. 4-((2-(2-(dimethylamino)ethyl)-1,3-dioxoisoindolin-6-ylamino)methyl)benzoic acid (282)

[0754] Title compound **282** was obtained by reacting the amine **281** with 4-formyl-benzoic acid, following the procedure described in the scheme 3, step 2 (example 12). ^1H NMR, (DMSO) δ (ppm): 7.89 (d, J = 8.2 Hz, 2H), 7.78 (t, J = 6.1 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 6.91 (s, 1H), 4.53 (d, J = 6.1 Hz, 2H), 3.80 (t, J = 5.5 Hz, 2H), 3.32 (bs, 2H), 3.21 (bs, 2H), 2.74 (s, 6H). LRMS: 367.4 (calc.); 368.4 (obt.) $(MH)^+$.

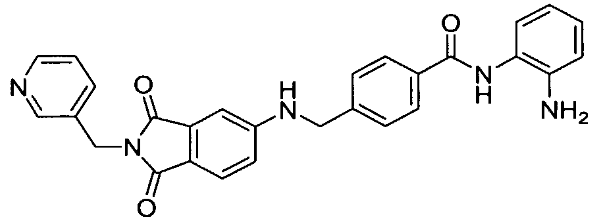
[0755] Step 4. 4-((2-(2-(dimethylamino)ethyl)-1,3-dioxoisoindolin-6-ylamino)methyl)-N-(2-aminophenyl) benzamide (278)

[0756] Title compound **278** was obtained by coupling of acid **282** with 1,2-phenylenediamine following the procedure described in the scheme 1, step 5 (example 1). ^1H NMR: (DMSO) δ (ppm): 9.52 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.63 (t, J = 5.9 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.05 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.82 (s, 1H), 6.76 (d, J = 8.2 Hz, 2H), 6.67 (d, J = 7.8 Hz, 1H), 6.49 (t, J = 7.2 Hz, 1H), 4.81 (s, 2H), 4.45 (d, J = 5.9 Hz, 2H), 3.48 (t, J = 6.3 Hz, 2H), 2.32 (t, J = 6.3 Hz, 2H), 2.04 (s, 6H). LRMS: (calc.) 457.5; (obt.) 458.5 $(MH)^+$.

Example 147

N-(2-Amino-phenyl)-4-[(1,3-dioxo-2-pyridin-3-ylmethyl-2,3-dihydro-1H-isoindol-5-ylamino)-methyl]-benzamide (283)

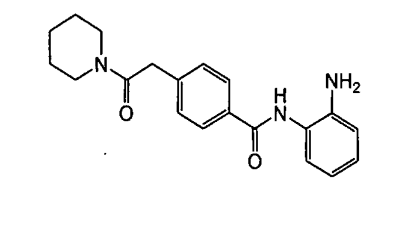
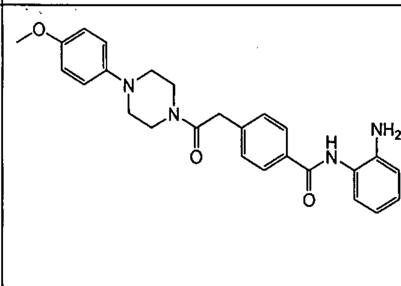
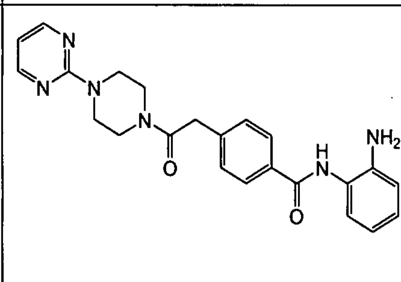
[0757] Title compound was prepared according to the reaction sequence depicted in scheme 58 for example 146, but using in the first step 3-aminomethylpyridine instead of N,N-dimethyl ethylenediamine.

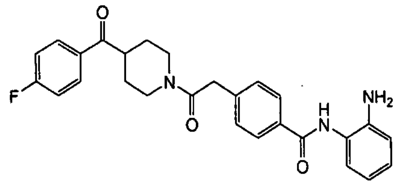
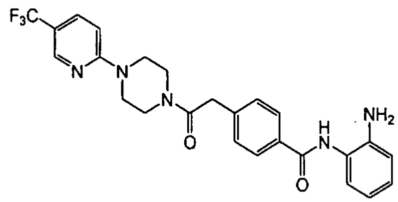
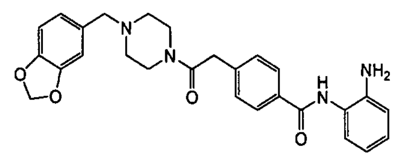


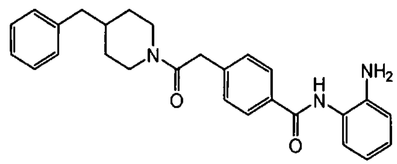
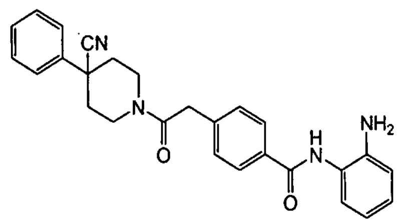
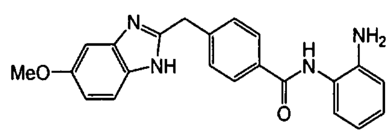
283: Example 147

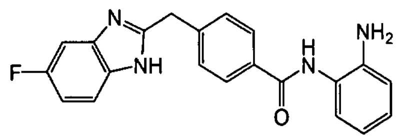
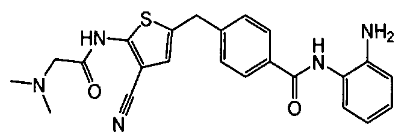
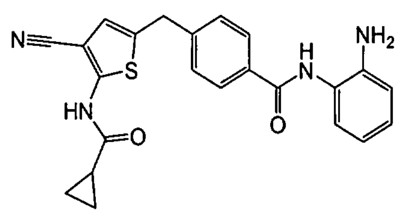
^{1}H NMR: (DMSO) δ (ppm): 9.60 (s, 1H), 8.50 (s, 1H), 8.44 (t, J = 3.7 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.76 (t, J = 6.3 Hz, 1H), 7.62 (dt, J = 2.0, 3.9 Hz, 2H), 7.54 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 4.7, 7.6 Hz, 1H), 7.12 (d, J = 6.6 Hz, 1H), 6.97-6.93 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.75 (dd, J = 1.4, 8.0 Hz, 1H), 6.58 (dt, J = 1.4, 7.6 Hz, 1H), 4.96 (bs, 2H), 4.70 (s, 2H), 4.53 (d, J = 6.3 Hz, 2H), LRMS: (calc.) 477.5; (obt.) 478.5 $(MH)^+$.

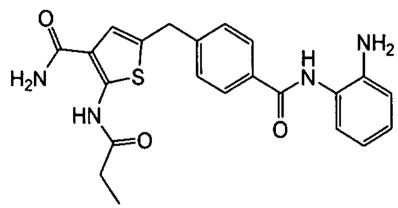
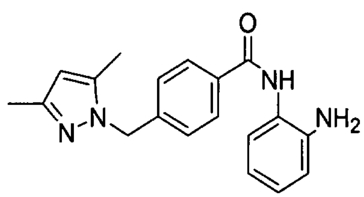
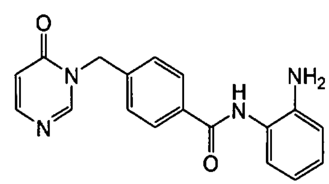
Table 10. Characterization of examples **148-177** (compounds **284-313**) prepared according to the schemes 19-30.

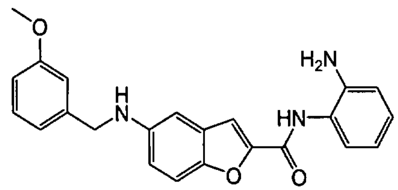
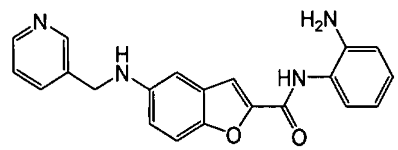
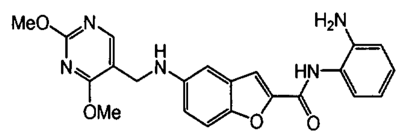
Ex	Cmpd	Structure	Name	Characterization
148	**284**		N-(2-Amino-phenyl)-4-(2-oxo-2-piperidin-1-yl-ethyl)-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.61 (bs, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H),7.14 (d, J = 7.6 Hz, 1H), 6.95 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.76 (dd, J = 8.0, 1.2 Hz, 1H), 6.58 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 4.89 (s, 2H), 3.78 (s, 2H), 3.44-3.42 (m, 4H), 1.56-1.54 (m, 2H), 1.41-1.36 (m, 4H). **MS**: (calc.) 337.2; (obt.) 338.4 $(MH)^{+}$.
149	**285**		N-(2-Amino-phenyl)-4-{2-[4-(4-methoxy-phenyl)-piperazin-1-yl]-2-oxo-ethyl}-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.60(s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 7.8 Hz, 1H), 6.93 (dd, J = 7.6, 7.6 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 6.78(d, J = 9.0 Hz, 2H), 6.74 (d, J = 7.8 Hz, 1H), 6.55 (dd, J = 7.4, 7.4 Hz, 1H), 4.88 (s, 2H), 3.83 (s, 2H), 3.65 (s, 3H), 3.62-3.58(m, 4H), 2.96-2.90 (m, 4H). **MS**: (calc.) 444.2; (obt.) 445.4 $(MH)^{+}$.
150	**286**		N-(2-Amino-phenyl)-4-[2-oxo-2-(4-pyrimidin-2-yl-piperazin-1-yl)-ethyl]-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.62 (s, 1H), 8.36 (d, J = 4.7 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 6.8 Hz, 1H), 6.95 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 6.76 (dd, J = 8.0, 1.4 Hz, 1H), 6.70 (t, J = 4.8 Hz, 1H), 6.57 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 4.90 (s, 2H), 3.87 (s, 2H), 3.72-3.68 (m, 4H), 3.62-3.55 (m, 4H). **MS**: (calc.) 416.2; (obt.) 417.4 $(MH)^{+}$.

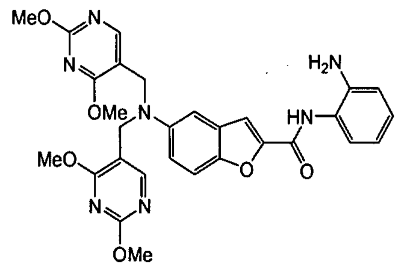
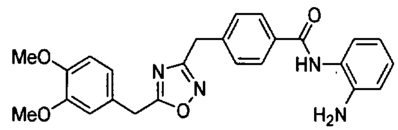
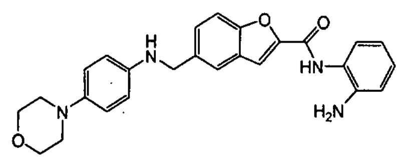
Ex	Cmpd	Structure	Name	Characterization
151	**287**		N-(2-Amino-phenyl)-4-{2-[4-(4-fluoro-benzoyl)-piperidin-1-yl]-2-oxo-ethyl}-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.62 (s, 1H), 8.08-8.04 (m, 2H), 7.91 (d, J = 8.0 Hz, 2H), 7.37-7.33 (m, 4H), 7.15 (d, J = 7.2 Hz, 1H), 6.95 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 6.76 (dd, J = 8.0, 1.4 Hz, 1H), 6.58 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 4.89 (s, 2H), 4.43-4.40 (m, 1H), 4.04-4.01 (m, 1H), 3.82 (s, 2H), 3.72-3.66 (m, 1H), 3.31-3.15 (m, 1H), 1.82-1.74 (m, 2H), 1.40-1.34 (m, 2H). **MS**: (calc.) 459.2; (obt.) 460.5 (MH)$^+$.
152	**288**		N-(2-Amino-phenyl)-4-{2-oxo-2-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.61 (s, 1H), 8.41 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.80 (dd, J = 9.3, 2.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 7.6 Hz, 1H), 6.97-6.93 (m, 2H), 6.76 (dd, J = 7.8, 1.4 Hz, 1H), 6.57 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 4.88 (s, 2H), 3.87 (s, 2H), 3.66-3.58 (m, 8H). **MS**: (calc.) 483.2; (obt.) 484.5 (MH)$^+$.
153	**289**		N-(2-Amino-phenyl)-4-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.60 (s, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 7.6 Hz, 1H), 6.95 (ddd, J = 7.6, 7.6, 1.8 Hz, 1H), 6.84-6.81 (m, 2H), 6.76 (dd, J = 7.8, 1.2 Hz, 1H), 6.72 (dd, J = 8.0, 1.6 Hz, 1H), 6.58 (ddd, J = 7.4, 7.4, 1.4 Hz, 1H), 5.97 (s, 2H), 4.89 (s, 2H), 3.78 (s, 2H), 3.49-3.46 (m, 4H), 3.37 (s, 2H), 2.29-2.27 (m, 4H). **MS**: (calc.) 372.2; (obt.) 373.5 (MH)$^+$.

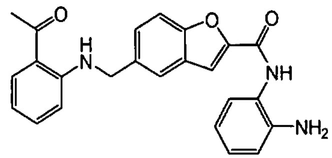
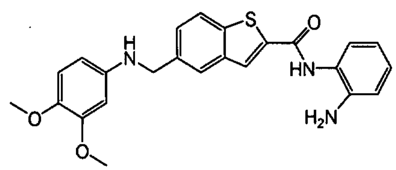
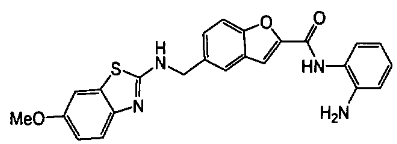
Ex	Cmpd	Structure	Name	Characterization
154	**290**		N-(2-Amino-phenyl)-4-[2-(4-benzyl-piperidin-1-yl)-2-oxo-ethyl]-benzamide	**^{1}H NMR: (400 MHz, DMSO-d$_6$, □ (ppm)**: 9.60 (s, 1H), 7.88 (d, J=8.2 Hz, 2H), 7.11 – 7.31 (m, 8H), 6.94 (d (dd), J=7.0 Hz, 1H), 6.75 (t (dd), J=7.8 Hz, 1H), 6.57 (d (dd), J=7.4 Hz, 1H), 4.87 (s, 2H), 4.34 (br. d, j = 12.5 Hz, 1H), 3.92 (br. d, j = 13.9 Hz, 1H), 3.75 (s, 2H), 3.32 (s, 2H), 2.91 (br. t, j = 11.3 Hz, 1H), 1.70-1.74 (m, 1H), 1.51-1.56 (m, 2H), 1.01 – 0.92 (m, 2H).
155	**291**		N-(2-Amino-phenyl)-4-[2-(4-cyano-4-phenyl-piperidin-1-yl)-2-oxo-ethyl]-benzamide	**^{1}H NMR: (400 MHz, DMSO-d$_6$, □ (ppm):** 9.60 (s, 1H), 7.90 (d, J=8.0 Hz, 2H), 7.33 – 7.51 (m, 7H), 7.13 (d (dd), J=7.4 Hz, 1H), 6.93 (t (dd), J=9.4 Hz, 1H), 6.74 (d (dd), J=8.0 Hz, 1H), 6.56 (t (dd), j = 7.8 Hz, 1H), 4.87 (s, 2H), 4.60 (br. d, j = 13.9 Hz, 1H), 4.17 (br. d, j = 14.7 Hz, 1H), 3.82 – 3.92 (m (instead of expected s), 2H), 3.26 (br. t, j = 12.1 Hz, 1H), 2.85 (br. t, j = 12.7 Hz, 1H), 2.12 – 2.16 (m, 2H), 1.89 – 1.94 (m, 2H).
156	**292**		N-(2-Amino-phenyl)-4-(5-methoxy-1H-benzoimidazol-2-ylmethyl)-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 12.12 (s, 1H), 9.59 (s, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.35 (s, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.97-6.93 (m, 2H), 6.77-6.73 (m, 2H), 6.58 (dd, J = 7.1, 7.1 Hz, 1H), 4.87 (s, 2H), 4.21 (s, 2H), 3.75 (s, 3H). **MS**: (calc.) 372.2; (obt.) 373.5 (MH)$^+$.

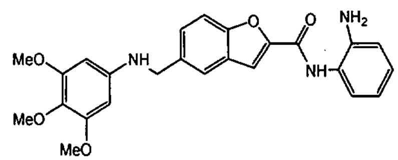
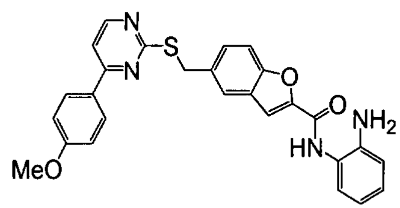
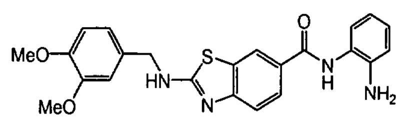
Ex	Cmpd	Structure	Name	Characterization
157	**293**		N-(2-Amino-phenyl)-4-(5-fluoro-1H-benzoimidazol-2-ylmethyl)-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 12.42 (s, 1H), 9.59 (s, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.43 (m, 3H), 7.26 (m, 1H), 7.13 (d, J = 6.7 Hz, 2H),6.23-6.99 (m, 2H), 6.74 (d, J = 1.4 Hz, 1H), 6.57 (dd, J = 8.2, 8.2 Hz, 1H), 4.87 (s, 2H), 4.24 (s, 2H), 3.16 (s, 1H). **MS**: (calc.) 360.1; (obt.) 361.5 $(MH)^+$.
158	**294**		N-(2-Amino-phenyl)-4-[4-cyano-5-(2-dimethylamino-acetylamino)-thiophen-2-ylmethyl]-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.60 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 7.3 Hz, 1H), 6.99-6.93 (m, 2H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 7.3, 7.3 Hz, 1H), 4.88 (bs, 2H), 4.12 (s, 2H), 3.33 (s, 2H), 2.36 (s, 6H). **MS**: (calc.) 432.2; (obt.) 433.5 $(MH)^+$.
159	**295**		N-(2-Amino-phenyl)-4-[4-cyano-5-(cyclopropanecarbonyl-amino)-thiophen-2-ylmethyl]-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 11.85 (bs, 1H), 9.61 (bs, 1H), 7.92 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 7.15 (d, J = 7.80 Hz, 1H), 6.98-6.95 (m, 2H), 7.11 (d, J = 8.8 Hz, 2H), 6.99 (dd, J = 7.7, 7.7 Hz, 1H), 6.77 (d, J = 6.3 Hz, 1H), 6.59 (dd, J = 7.6, 7.6 Hz, 1H), 4.88 (bs, 2H), 4.12 (s, 2H), 2.14-2.13 (m, 1H), 0.90-0.84 (m, 4H). **MS**: (calc.) 392.1; (obt.) 393.4 $(MH)^+$.

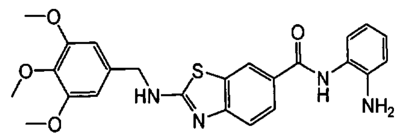
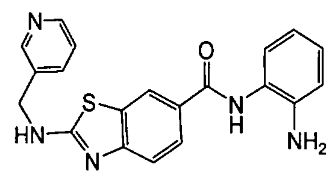
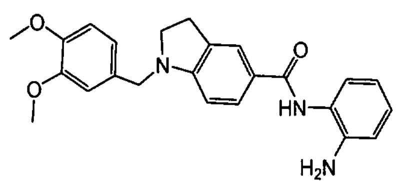
Ex	Cmpd	Structure	Name	Characterization
160	**296**		5-[4-(2-Amino-phenylcarbamoyl)-benzyl]-2-propionylamino-thiophene-3-carboxylic acid amide	**^{1}H NMR: (DMSO) δ (ppm):** 12.06 (s, 1H), 9.61(s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.82 (bs, 1H), 7.45 (bs, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.19 (s, 1H), 7.14 (d, J = 6.2 Hz, 1H), 6.95 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 6.76 (dd, J = 8.2, 1.6 Hz, 1H), 6.57 (ddd, J = 7.4, 7.4, 1.6 Hz, 1H), 4.98 (s, 2H), 4.10 (s, 2H), 2.44 (q, J = 7.6 Hz, 2H), 1.09 (t, J = 7.6 Hz, 2H). **MS**: (calc.) 422.1.; (obt.) 423.4. (MH)$^+$.
161	**297**		N-(2-Amino-phenyl)-4-(3,5-dimethyl-pyrazol-1-ylmethyl)-benzamide	**^{1}H NMR: (400 MHz, DMSO-d$_6$, □ (ppm):** 9.59 (s, 1H), 7.92 (d, J=8.2, 2H), 7.16 (d, J=8.4, 2H), 7.12 (d (dd), J=6.5, 1H), 6.94 (dd, J=1.4 Hz, j = 7.8 Hz, 1H), 6.75 (dd, j = 1.4 Hz, j = 8.0 Hz, 1H), 6.57 (dd, j = 1.4 Hz, 7.4 Hz, 1H), 5.86 (s, 1H), 5.26 (s, 2H), 4.88 (s, 2H), 2.16 (s, 3H), 2.11 (s, 3H)
162	**298**		N-(2-Amino-phenyl)-4-(6-oxo-6H-pyrimidin-1-ylmethyl)-benzamide	**^{1}H NMR: (DMSO) δ (ppm):** 9.61 (s, 1H), 8.69 (s, 1H), 7.94-7.92 (m, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 7.4 Hz, 1H), 6.95 (dd, J = 7.2, 7.2 Hz, 1H), 6.75 (d, J = 7.2 Hz, 1H), 6.57 (dd, J = 7.2, 7.2 Hz, 1H), 5.16 (s, 2H), 4.89 (s, 2H). **MS**: (calc.) 320.2; (obt.) 321.5 (MH)$^+$.

Ex	Cmpd	Structure	Name	Characterization
163	**299**		5-(3-Methoxy-benzylamino)-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.69 (s, 1H), 7.45 (s, 1H), 7.40 (d, J = 6.8 Hz, 1H), 7.26-7.18 (m, 2H), 6.97-6.73 (m, 8H), 6.60 (dd, J = 7.3, 7.3 Hz, 1H), 6.22 (t, J = 5.9 Hz, 1H), 4.92 (s, 2H), 4.27 (d, J = 5.9 Hz, 2H), 3.73 (s, 3H). **MS**: (calc.) 387.1; (obt.) 388.4 $(MH)^{+}$.
164	**300**		5-[(Pyridin-3-ylmethyl)-amino]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.69 (s, 1H), 8.62 (s, 1H), 8.44 (d, J = 4.4 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 8.1, 5.1 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 6.97 (dd, J = 7.0, 7.0 Hz, 1H), 6.88 (dd, J = 8.8, 2.2 Hz, 1H), 6.79-6.77 (m, 2H), 6.59 (dd, J = 6.9, 6.9 Hz, 1H), 6.27 (t, J = 5.9 Hz, 1H), 4.91 (s, 2H), 4.33 (d, J = 5.9 Hz, 1H). **MS**: (calc.) 358.1; (obt.) 359.4 $(MH)^{+}$.
165	**301**		5-[(2,4-Dimethoxy-pyrimidin-5-ylmethyl)-amino]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.70 (s, 1H), 8.20 (s, 1H), 7.46 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.17 (dd, J = 7.8, 1.2 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.85 (dd, J = 8.9, 2.3 Hz, 1H), 6.78-6.76 (m, 2H), 6.58 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 5.99 (t, J = 5.8 Hz, 1H), 4.92 (s, 2H), 4.14 (d, J = 5.9 Hz, 2H), 3.97 (s, 3H), 3.86 (s, 3H). **MS**: (calc.) 419.2; (obt.) 420.5 $(MH)^{+}$.

Ex	Cmpd	Structure	Name	Characterization
166	**302**		5-[Bis-(2,4-dimethoxy-pyrimidin-5-ylmethyl)-amino]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.72(s, 1H), 7.66 (s, 2H), 7.47-7.39 (m, 2H), 7.15 (d, J = 7.0 Hz, 1H), 6.98-6.92 (m, 3H), 6.75 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 7.5, 7.5 Hz, 1H), 4.91 (s, 2H), 4.47(s, 4H), 3.90 (s, 6H), 3.82 (s, 6H). **MS**: (calc.) 571.2; (obt.) 572.5 $(MH)^+$.
167	**303**		N-(2-Amino-phenyl)-4-[5-(3,4-dimethoxy-benzyl)-[1,2,4]oxadiazol-3-ylmethyl]-benzamide	**^{1}H NMR: (300 MHz, DMSO-d_6, □ (ppm):** 9.61 (s, 1H), 7.92 (d, J=7.62, 2H), 7.42 (d, J=8.21, 2H), 7.15 (d, J=7.62, 1H), 6.99-6.89 (m, 3H), 6.83-6.76 (m, 2H), 6.59 (t, J=7.03, 1H), 4.88 (brs, 2H), 4.23 (s, 2H), 4.16 (s, 2H), 3.72 (s, 3H), 3.71 (s, 3H)
168	**304**		5-[(4-Morpholin-4-yl-phenylamino)-methyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.01 (s, 1H), 6.92 (s, 1H), 6.84 (s, 1H), 6.80 (d, J=8.5, 1H), 6.65 (d, J=9.0, 1H), 6.36 (d, J=8.0, 1H), 6.16 (t, J=7.75, 1H), 5.96 (d, J=7.5, 1H), 5.89 (d, J=8.0, 2H), 5.77 (t, J=7.5, 1H), 5.71 (d, J=8.0, 2H), 5.05 (m, 1H), 4.12 (brs, 2H), 3.49 (brd, J=5.5, 2H), 2.87-2.83 (m, 4H), 2.06-2.02 (m, 4H). **MS**: (calc.) 442; (obt.) 443.5 $(MH)^+$.

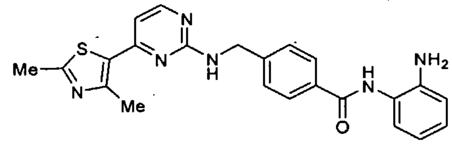
Ex	Cmpd	Structure	Name	Characterization
169	305		5-[(2-Acetyl-phenylamino)-methyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.85 (s, 1H), 9.26 (s, 1H), 7.86 (d, J=8.0, 1H), 7.75 (s, 1H), 7.69-7.67 (m, 2H), 7.47 (d, J=8.5, 1H), 7.33 (t, J=7.75, 1H), 7.19 (d, J=7.5, 1H), 6.99 (t, J=7.75, 1H), 6.78 (d, J=14.0, 1H), 6.77 (d, J=14.0, 1H), 6.62-6.59 (m, 2H), 4.96 (s, 2H), 4.59 (d, J=5.5, 2H), 2.57 (s, 3H). **MS**: (calc.) 399; (obt.) 400.2 $(MH)^+$.
170	306		5-[(3,4-Dimethoxy-phenylamino)-methyl]-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.88 (s, 1H), 8.25 (s, 1H), 7.97 (d, J=8.5, 1H), 7.91 (s, 1H), 7.49 (d, J=8.5, 1H), 7.16 (d, J=7.5, 1H), 6.98 (t, J=7.25, 1H), 6.78 (d, J=8.0, 1H), 6.65 (d, J=8.0, 1H), 6.60 (t, J=7.5, 1H), 6.35 (s, 1H), 6.05 (d, J=9.0, 1H), 5.96 (s, 1H), 4.97 (s, 2H), 4.36 (d, J=5.0, 2H), 3.65 (s, 3H), 3.58 (s, 3H). **MS**: (calc.) 433.1; (obt.) 434.5 $(MH)^+$.
171	307		5-[(6-Methoxy-benzothiazol-2-ylamino)-methyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**MS**: (calc.) 444.1; (obt.) 445.4 $(MH)^+$.

Ex	Cmpd	Structure	Name	Characterization
172	**308**		5-[(3,4,5-Trimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.82 (s, 1H), 7.75 (s, 1H); 7.67 (s, 1H); 7.63 (d, J=8.6 Hz, 1H); 7.47 (dd, J=8.6, 1.6 Hz, 1H); 7.16 (dd, J= 7.8, 1.4, Hz, 1H); 6.96 (dt, J=8.0, 1.6 Hz, 1H); 6.76 (dd, J=8.0, 1.4 Hz, 1H); 6.58 (dt, J= 7.6, 1.4 Hz, 1H); 6.11 (t, J = 6.1 Hz, 1H); 5.90 (s, 2H); 4.95 (s, 2H); 4.34 (d, J= 5.9 Hz, 2H); 3.63 (s, 6H); 3.49 (s, 3H). **MS**: (calc.) 447.2; (obt.) 448.5 $(MH)^+$.
173	**309**		5-[4-(4-Methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.85 (s, 1H), 8.63 (d, J=5.3 Hz, 1H), 8.19 (dd, J= 6.8, 2.0 Hz, 2H); 7.89 (d, J=1.0 Hz, 1H); 7.73 (d, J=5.5 Hz, 1H); 7.66 (m, 2H); 7.59 (dd, J= 8.6, 1.8 Hz, 1H); 7.17 (dd, J= 7.6, 1.2 Hz, 1H); 7.10 (dd, J= 6.8, 2.0 Hz, 2H); 6.98 (dt, J= 8.0, 1.8 Hz, 1H); 6.78 (dd, J= 7.8, 1.2 Hz, 1H); 6.59 (ddd, J=1.4, 7.6, 8.8 Hz, 1H); 4.97 (s, 2H); 4.64 (s, 2H); 3.86 (s, 3H). **MS**: (calc.) 482.5; (obt.) 483.5 $(MH)^+$.
174	**310**		2-(3,4-Dimethoxy-benzylamino)-benzothiazole-6-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 948 (s, 1H), 8.00 (d, J=2.0, 1H), 7.77 (dd, J=8 .2, 1.6, 1H), 7.11 (d, J= 6.7, 1H), 7.06-7.04 (m, 2H), 6.92 (dt, J = 7.6, 1.6 Hz, 1H), 6.86-6.84 (m, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.73 (dd, J= 8.2, 1.6 Hz, 6.55 (dt, J = 7.6, 1.2 Hz, 1H), 5.11 (s, 2H), 4.86 (brs, 2H), 3.71 (s, 3H), 3.69 (s, 3H). **MS**: (calc.) 434; (obt.) 435.4 $(MH)^+$.

Ex	Cmpd	Structure	Name	Characterization
175	**311**		2-(3,4,5-Trimethoxy-benzylamino)-benzothiazole-6-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.54 (s, 1H), 8.70 (brt, J=5.48, 1H), 8.30 (d, J=1.76, 1H), 7.86 (dd, J=8.32, 1.67, 1H), 7.45 (d, J=8.41, 1H), 7.15 (d, J=6.85, 1H), 6.94 (m, 1H), 6.76 (dd, J=7.93, 1.27, 1H), 6.72 (s, 2H), 6.58 (m, 1H), 4.89 (brs, 2H), 4.55 (d, J=5.48, 2H), 3.76 (s, 6H), 3.63 (s, 3H). **MS**: (calc.) 464; (obt.) 465.5 $(MH)^+$.
176	**312**		2-[(Pyridin-3-ylmethyl)-amino]-benzothiazole-6-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.56 (s, 1H), 8.83 (t, J=5.9 Hz, 1H); 8.62 (d, J=1.4 Hz, 1H); 8.49 (dd, J=1.6, 4.7 Hz, 1H); 8.32 (d, J=1.8 Hz, 1H); 7.88 (dd, J=1.9, 6.4 Hz, 1H); 7.81 (m, 1H); 7.40 (m, 1H); 7.46 (d, J=8.4 Hz, 1H); 7.16 (d, J=6.4 Hz, 1H); 6.96 (dt, J=1.0, 8.6 Hz, 1H); 6.77 (dd, J=1.2, 7.8 Hz, 1H); 6.60 (dt, J=1.0, 8.8 Hz, 1H); 4.90 (s, 2H); 4.68 (d, J=5.7 Hz, 2H). **MS**: (calc.) 375.1; (obt.) 376.4 $(MH)^+$.
177	**313**		1-(3,4-Dimethoxy-benzyl)-2,3-dihydro-1H-indole-5-carboxylic acid (2-amino-phenyl)-amide	**^{1}H NMR: (DMSO) δ (ppm):** 9.29 (s, 1H), 7.71 (dd, J=8.22, 1.77, 1H), 7.66 (brm, 1H), 7.12 (dd, J=7.93, 1.47, 1H), 6.93-6.89 (m, 3H), 6.84 (dd, J=8.22, 1.96, 1H), 6.75 (dd, J=8.02, 1.37, 1H), 6.65 (d, J=8.41, 1H), 6.57 (dt, J=7.53, 1.30, 1H), 4.82 (s, 2H), 3.73 (s, 6H), 3.41 (t, J=8.51, 2H), 2.98 (t, J=8.51, 2H). **MS**: (calc.) 403; (obt.) 404.5 $(MH)^+$.

Example 178:

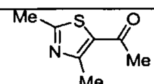
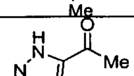
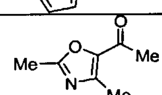
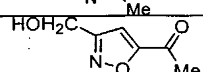
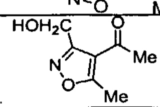
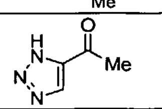
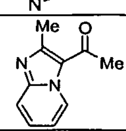
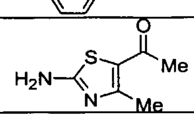
N-(2-Amino-phenyl)-4-{[4-(2,4-dimethyl-thiazol-5-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (314)



314: Example 178

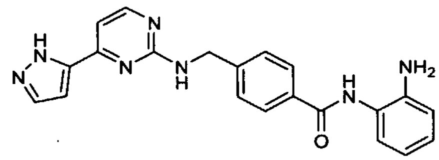
[0758] Title compound was obtained according to the scheme 6 similarly to the compound **26a** (**Example 29**) using instead of 1-pyrazin-2-yl-ethanone as the starting material 1-(2,4-dimethyl-thiazol-5-yl)-ethanone (Table 11). Characterization of the title compound is provided in the Table 12.

Table 11. Heteroarylmethyl ketones used in the synthesis of examples **178 - 188**

Cmpd	Structure of Heteroarylmethyl ketone	Name of the Heteroarylmethyl ketone	Scheme	Example of the final product it was used for
		1-(2,4-Dimethyl-thiazol-5-yl)-ethanone		**178**
		1-(2H-Pyrazol-3-yl)-ethanone		**179**
		1-(2,4-Dimethyl-oxazol-5-yl)-ethanone		**180**
320		1-(3-Hydroxymethyl-isoxazol-5-yl)-ethanone	**59**	**181**
324		1-(3-(Hydroxymethyl)-5-methylisoxazol-4-yl)ethanone	**60**	**182**
327		1-(3*H*-1,2,3-Triazol-4-yl)ethanone	**61**	**183, 184**
333		1-(2-Methylimidazo[1,2-a]pyridin-3-yl)ethanone	**62**	**185**
		1-(2-Amino-4-methylthiazol-5-yl)ethanone		**186, 187**

Example 179:

N-(2-Amino-phenyl)-4-{[4-(2H-pyrazol-3-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (315)

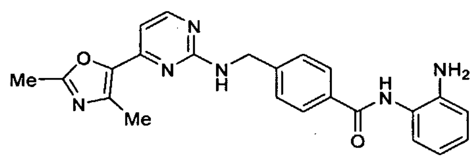


315: Example 179

[0759] Title compound was obtained according to the scheme 6 similarly to the compound **26a** (**Example 29**) using instead of 1-pyrazin-2-yl-ethanone as the starting material 1-(2*H*-pyrazol-3-yl)-ethanone (Table 11). Characterization of the title compound is provided in the Table 12.

Example 180:

N-(2-Amino-phenyl)-4-{[4-(2,4-dimethyl-oxazol-5-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (316)

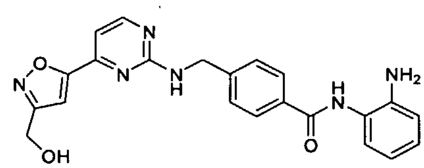


316: Example 180

[0760] Title compound was obtained according to the scheme 6 similarly to the compound **26a** (**Example 29**) using instead of 1-pyrazin-2-yl-ethanone as the starting material 1-(2,4-dimethyl-oxazol-5-yl)-ethanone (Table 11). Characterization of the title compound is provided in the Table 12.

Example 181:

N-(2-Amino-phenyl)-4-{[4-(2,4-dimethyl-oxazol-5-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (317)



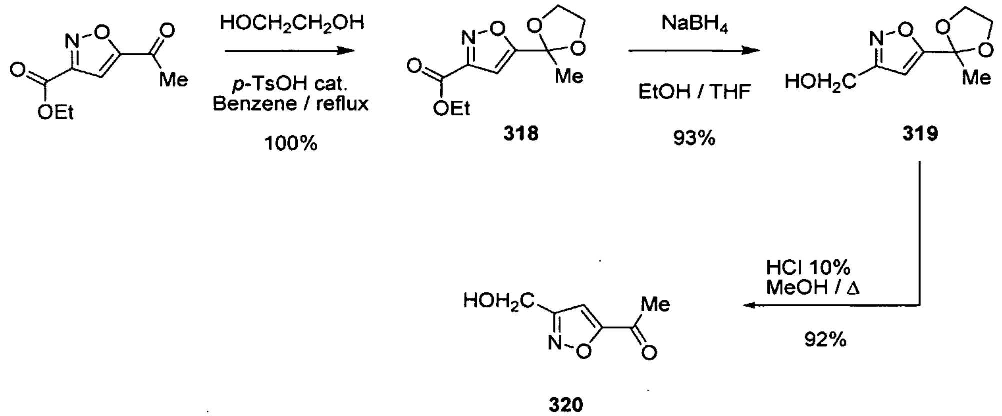
317: Example 181

[0761] Step 1. Ethyl 5-(2-methyl-1,3-dioxolan-2-yl)isoxazole-3-carboxylate (318)

[0762] A reaction mixture consisting of ethyl 5-acetylisoxazole-3-carboxylate (2.53 g, 13.8 mmol), ethylene glycol (1.29 g, 20.7 mmol,) and *p*-TsOH (0.13 g, 0.69 mmol,) in benzene (50 mL) was refluxed with the Dean-Stark adapter for 24 hours (scheme 59). Most of the solvent was

removed under reduced pressure and the residue was partitioned between saturated $NaHCO_3$ and EtOAc. Organic layer was collected, washed with brine, water, and dried over $MgSO_4$. Evaporation of the dried extract under reduced pressure afforded the title compound as an oil (3.14 g, 100% yield), which was used for next step without further purification. ^1H NMR (DMSO-d_6) δ (ppm): 6.89 (s, 1H), 4.35 (q, J=7.2 Hz, 2H), 4.07-4.01 (m, 2H), 4.01-3.94 (m, 2H), 1.70 (s, 3H), 1.32 (t, J=7.0 Hz, 3H). MS (m/z): 227.21 (calc) 228.1 (MH+) (found).

Scheme 59.



[0763] Step 2. (5-(2-Methyl-1,3-dioxolan-2-yl)isoxazol-3-yl)methanol (319)

[0764] To a solution of the dioxolane **318** (3.14 g, 13.8 mmol) in a 1:2 mixture of EtOH – THF (45 mL) $NaBH_4$ (0.68 g, 18.0 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours, treated with water and the organic solvents were evaporated. The aqueous phase was extracted with EtOAc and combined organic layers were successively washed with H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as oil (2.39 g, 93% yield) which was used for next step without further purification. ^1H NMR (DMSO-d_6) δ (ppm): 6.43 (s, 1H), 5.47 (t, J=5.9 Hz, 1H), 4.47 (d, J=5.9 Hz, 2H), 4.06-4.02 (m, 2H), 3.94-3.90 (m, 2H), 1.66 (s, 3H). MS (m/z): 185.18 (calc) 186.1 (MH+) (found).

[0765] Step 3. 1-(3-(Hydroxymethyl)isoxazol-5-yl)ethanone (320)

[0766] To a solution of the carbinol **319** (2.39 g, 12.9 mmol) in MeOH (30 mL) 10% HCl (30 mL) was added. The reaction mixture was stirred at 70°C for 18 hours, cooled and neutralized to pH 6 using 1M NaOH solution. MeOH was evaporated and the resulting aqueous phase was extracted with EtOAc. The organic layer was washed with brine, dried under $MgSO_4$ and concentrated under reduced pressure to produce the title compound as a beige solid (1.67 g, 92% yield), which was used for next step without further purification. ^1H NMR (DMSO-d_6) δ (ppm):

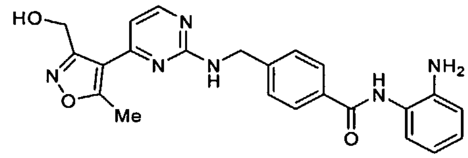
7.25 (s, 1H), 5.62 (t, J=6.1 Hz, 1H), 4.56 (d, J=5.9 Hz, 2H), 2.56 (s, 3H). MS (m/z): 141.12 (calc) 142.1 (MH+) (found)

[0767] Step 4. N-(2-Amino-phenyl)-4-{[4-(2,4-dimethyl-oxazol-5-yl)-pyrimidin-2-ylamino]-methyl}-benzamide (317)

[0768] Title compound was obtained according to the scheme 6 similarly to the compound **26a** (Example 29) using instead of 1-pyrazin-2-yl-ethanone as the starting material the ketone **320** (Table 11). Structure and characterization of the title compound are presented in the Table 12.

Example 182:

N-(2-aminophenyl)-4-((4-(3-(hydroxymethyl)-5-methylisoxazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide (321)



321: Example 182

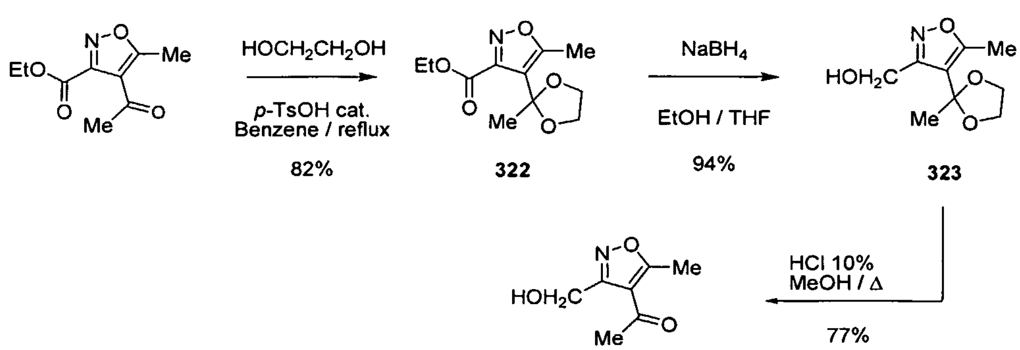
[0769] Step 1. Methyl 5-methyl-4-(2-methyl-1,3-dioxolan-2-yl)-isoxazole-3-carboxylate (322)

[0770] Title compound was obtained similarly to the dioxolane **318** in 82% yield according to the scheme 60. MS (m/z): 227.21 (calc) 228.1 (MH+) (found)

[0771] Step 2. (5-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)isoxazol-3-yl)methanol (323)

[0772] Title compound was obtained similarly to the carbinol **319** in 94% yield according to the scheme 60. ^{1}H NMR (DMSO-d_6) δ(ppm): 5.21 (t, J=5.7 Hz, 1H), 4.48 (d, J=5.7 Hz, 2H), 3.98-3.94 (m, 2H), 3.71-3.67 (m, 2H), 2.39 (s, 3H), 1.60 (s, 3H). MS (m/z): 199.20 (calc) 200.1 (MH+) (found)

Scheme 60



[0773] Step 3. 1-(3-(Hydroxymethyl)-5-methylisoxazol-4-yl)ethanone (324)

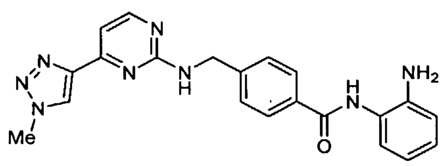
[0774] Title compound was obtained similarly to the ketone **320** in 77% yield according to the scheme 60. ^{1}H NMR (DMSO-d_6) δ (ppm): 5.45 (t, J=5.9 Hz, 1H), 4.66 (d, J=5.9 Hz, 2H), 2.66 (s, 3H), 2.51 (s, 3H). MS (m/z): 155.15 (calc) 156.1 (MH+) (found)

[0775] Step 4. N-(2-aminophenyl)-4-((4-(3-(hydroxymethyl)-5-methylisoxazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide (317)

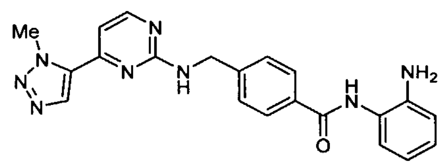
[0776] Title compound was obtained according to the scheme 6 similarly to the compound **26a** (Example 29) using instead of 1-pyrazin-2-yl-ethanone as the starting material the ketone **324** (Table 11). Characterization of the title compound is provided in the Table 12.

Examples 183, 184:

N-(2-aminophenyl)-4-((4-(1-methyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide (325) and N-(2-aminophenyl)-4-((4-(3-methyl-3H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide (326)



325: Example 183

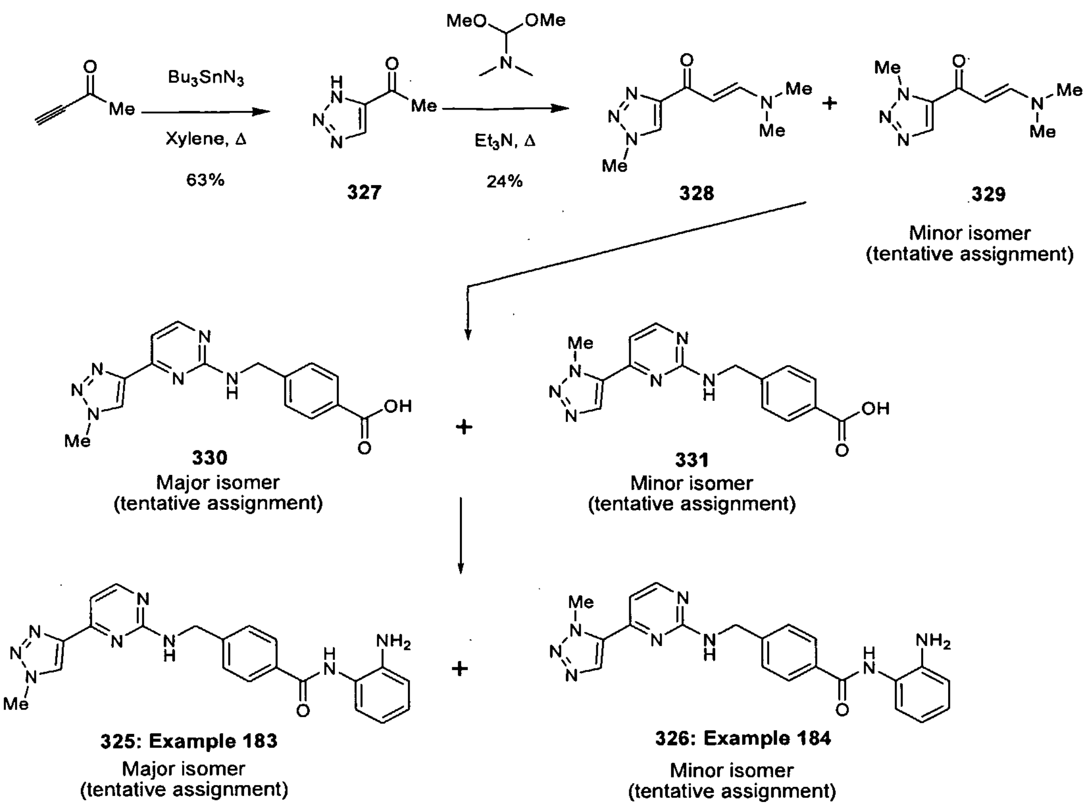


326: Example 184

[0777] Step 1. 1-(3H-1,2,3-Triazol-4-yl)ethanone (327).

[0778] To a solution of 3-butyn-2-one (627 mg, 9.21 mmol) in xylene (10 mL) was added azidotributyltin (4.00 g, 12.0 mmol). The reaction mixture was stirred at 140°C for 3 hours in a sealed flask. Xylene was evaporated and the residue was purified by flash chromatograpy, eluent EtOAc to afford the title compound (645 mg, 63% yield). ^{1}H NMR (DMSO-d_6) δ(ppm): 8.51 (s, 1H), 2.56 (s, 3H). MS (m/z): 111.10 (calc) 112.1 (MH+) (found)

Scheme 61



[0779] Step 2. (E)-3-(dimethylamino)-1-(1-methyl-1H-1,2,3-triazol-4-yl)prop-2-en-1-one (328) and (E)-3-(dimethylamino)-1-(3-methyl-3H-1,2,3-triazol-4-yl)prop-2-en-1-one (329)

[0780] Mixture of title compounds **328** and **329** was obtained in 24% yield according to the scheme 6 similarly to the compound **23a** (Example 29, step 1) using instead of 1-pyrazin-2-yl-ethanone as the starting material ketone **327** (Table 11). MS (m/z): 180.21 (calc) 181.1 (MH+) (found).

[0781] ^{1}H NMR (DMSO-d_6) δ (ppm) (**328**, major isomer, tentative assignment): 8.01 (s, 1H), 7.74 (d, J=12.3 Hz, 1H), 5.73 (d, J=12.3 Hz, 1H), 4.18 (s, 3H), 3.15 (s, 3H), 2.88 (s, 3H).

[0782] ^{1}H NMR (DMSO-d_6) δ (ppm) (**329**, minor isomer, tentative assignment): 8.26 (s, 1H), 7.71 (d, J=10.8 Hz, 1H), 5.66 (d, J=12.1 Hz, 1H), 4.19 (s, 3H), 3.16 (s, 3H), 2.92 (s, 3H).

[0783] Step 3. 4-((4-(1-Methyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino) methyl)benzoic acid (330) and 4-((4-(3-methyl-3H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzoic acid (331).

[0784] Mixture of title compounds was obtained in 80% yield according to the scheme 6 similarly to the compound **25a** (Example 29, step 3) using instead of enamino ketone **23a** as a starting material mixture of enamino ketones **328** and **329**. ^{1}H NMR (DMSO-d_6) δ (ppm) (**328**,

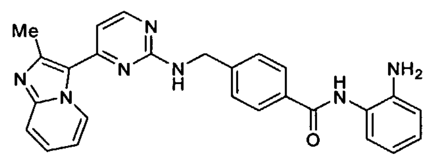
major isomer, tentative assignment): 12.80 (s, 1H), 8.33 (d, J=5.1 Hz, 1H), 8.17 (s, 1H), 7.94 (t, J=6.5 Hz, 1H), 7.85 (d, J=8.2 Hz, 2H), 7.42 (d, J=8.2 Hz, 2H), 7.02 (d, J=4.7 Hz, 1H), 4.60 (d, J=6.5 Hz, 2H), 4.22 (s, 3H). MS (m/z): 310.31 (calc) 311.2 (MH+) (found)

[0785] Step 4. N-(2-aminophenyl)-4-((4-(1-methyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide (325) and N-(2-aminophenyl)-4-((4-(3-methyl-3H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide (326)

[0786] Title compounds were obtained in 53 and 7% yields according to the scheme 6 similarly to the compound **26a** (Example 29, step 4) using instead of acid **25a** as a starting material mixture of acids **330** and **331**. Characterization of the title compounds is provided in the Table 12.

Example 185:

N-(2-Aminophenyl)-4-((4-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-2-ylamino)methyl)benzamide (332)



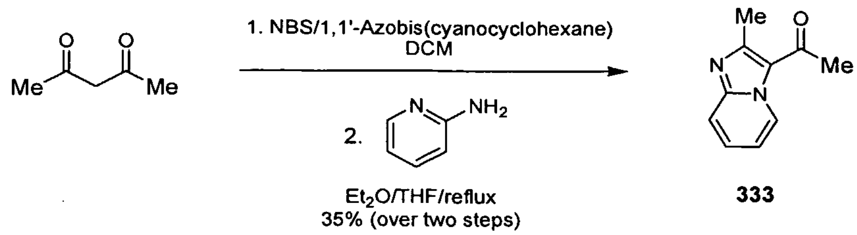
332: Example 185

[0787] Step 1. 1-(2-Methylimidazo[1,2-a]pyridin-3-yl)ethanone (333)

[0788] 1,1'-Azobis(cyclohexanecarbonitrile) (catalytic amount) was added to a solution of pentane-2,4-dione (1.00 g, 9.99 mmol) and N-bromosuccinimide (1.96 g, 10.99 mmol) in $CHCl_3$ (20 mL). The reaction mixture was stirred for 1 hour, filtered and the filtrate was concentrated under reduced pressure. The residue was re-dissolved in a 1:1 mixture of THF / Et_2O (20 mL), then pyridin-2-amine (723 mg, 7.68 mmol) was added and the reaction mixture was refluxed overnight. After cooling the solvent was removed under reduced pressure and the residue was purified by column chromatography, eluents EtOAc, then EtOAc-MeOH (96:4), to afford the title compound (475 mg 35 % yield). ^1H NMR (DMSO-d_6) δ (ppm): 9.59 (dt, J=6.8, 1.4 Hz, 1H), 7.68 (dt, J=8.8, 1.2 Hz, 1H), 7.56 (ddd, J=8.8, 6.8, 1.4 Hz, 1H), 7.17 (td, J=6.8, 1.4 Hz, 1H), 2.72 (s, 3H), 2.58 (s, 3H). MS (m/z): 174.20 (calc) 175.1 (MH+) (found).

[M. Anderson, J. F. Beattie, *et. al.* Bioorg. Med. Chem. Lett.; 2003, *13*; 3021-3026].

Scheme 62.



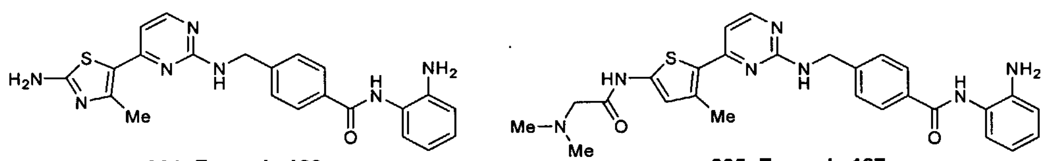
333

[0789] Step 2. N-(2-Aminophenyl)-4-((4-(2-methylimidazo[1,2-a]pyridin-3-yl)pyrimidin-2-ylamino)methyl)benzamide (332)

[0790] Title compound was obtained according to the scheme 6 similarly to the compound **26a** (**Example 29**) using instead of 1-pyrazin-2-yl-ethanone as the starting material the ketone **333** (Table 11). Characterization of the title compound is provided in the Table 12.

Examples 186 and 187

4-((4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-ylamino)methyl)-N-(2-aminophenyl)benzamide (334) and N-(2-aminophenyl)-4-((4-(5-(2-(dimethylamino)acetamido)-3-methylthiophen-2-yl)pyrimidin-2-ylamino)methyl)benzamide (335)



334: Example 186

335: Example 187

[0791] Step 1. 2-(bis-Boc-Amino-)-5-acetyl-4-methylthiazole (336)

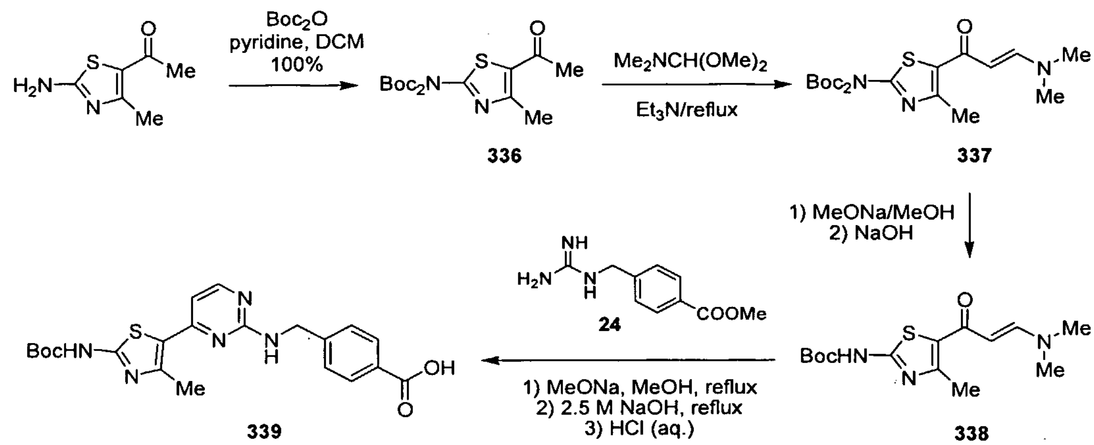
[0792] Pyridine (1.11 g, 14.1 mmol) was added to a solution of Boc_2O (3.07 g, 14.1 mmol) and 1-(2-amino-4-methylthiazol-5-yl) (2.00 g, 12.8 mmol) in DCM (20 mL). The reaction mixture was stirred for 3 days at room temperature. The same amount of Boc_2O was added and the reaction mixture was stirred for another 3 days. DCM was evaporated under reduced pressure, water was added and the resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as orange oil (4.6 g, 100% yield). ^1H NMR (DMSO-d_6) δ (ppm): 2.54 (s, 3H), 2.49 (s, 3H), 1.53 (s, 18H). MS (m/z): 356.44 (calc) 357.1 (MH+) (found)

[0793] Step 2. (E)-1-[2-(bis-Boc-Amino-)-4-methylthiazol-5-yl]-3-(dimethylamino)prop-2-en-1-one (337)

[0794] Following the procedure described for the synthesis of enamino ketone **23a** (scheme 6) but substituting 1-(pyrazin-2-yl)-ethanone for the ketone **336**, title compound was obtained in

16% yield. ^{1}H NMR (DMSO-d_6) δ (ppm): 7.65 (d, J=12.1 Hz, 1H), 5.34 (d, J=12.1 Hz, 1H), 3.14 (s, 3H), 2.87 (s, 3H), 2.50 (s, 3H), 1.51 (s, 18H). MS (m/z): 411.52 (calc) 412.3 (MH+) (found).

Scheme 63



[0795] Step 3. (E)-1-[2-(Boc-Amino-)-4-methylthiazol-5-yl]-3-(dimethylamino)prop-2-en-1-one (338)

[0796] A solution of enamino ketone **337** (859 mg, 2.09 mmol) in methanol (12 mL) was treated with NaOMe solution (25% ww, 1.9 ml). The reaction mixture refluxed for 24 hours, treated with NaOH solution (1M, 3 ml), cooled to the room temperature, carefully neutralized (pH 7.5-8) with 1M HCl and extracted with EtOAc. Extract was dried over $MgSO_4$, filtered and evaporated to provide a residue corresponding to the title compound (721 mg, more than quantitative yield), which was used for the next step without further purification. MS (m/z): 311.40 (calc) 312.1 (MH+) (found).

[0797] Step 4. 4-((4-(2-(tert-Butoxycarbonylamino)-4-methylthiazol-5-yl)pyrimidin-2-ylamino)methyl)benzoic acid (339).

[0798] Following the procedure described for the synthesis of the acid **25a** (scheme 6, step 3) but substituting enamino ketone **23a** for the enamino ketone **338**, title compound was obtained in 18% yield and was used for the next steps without further purification. MS (m/z): 441.50 (calc) 442.3 (MH+) (found).

[0799] Steps 5 and 6. 4-((4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-ylamino)methyl)-N-(2-aminophenyl)benzamide (334).

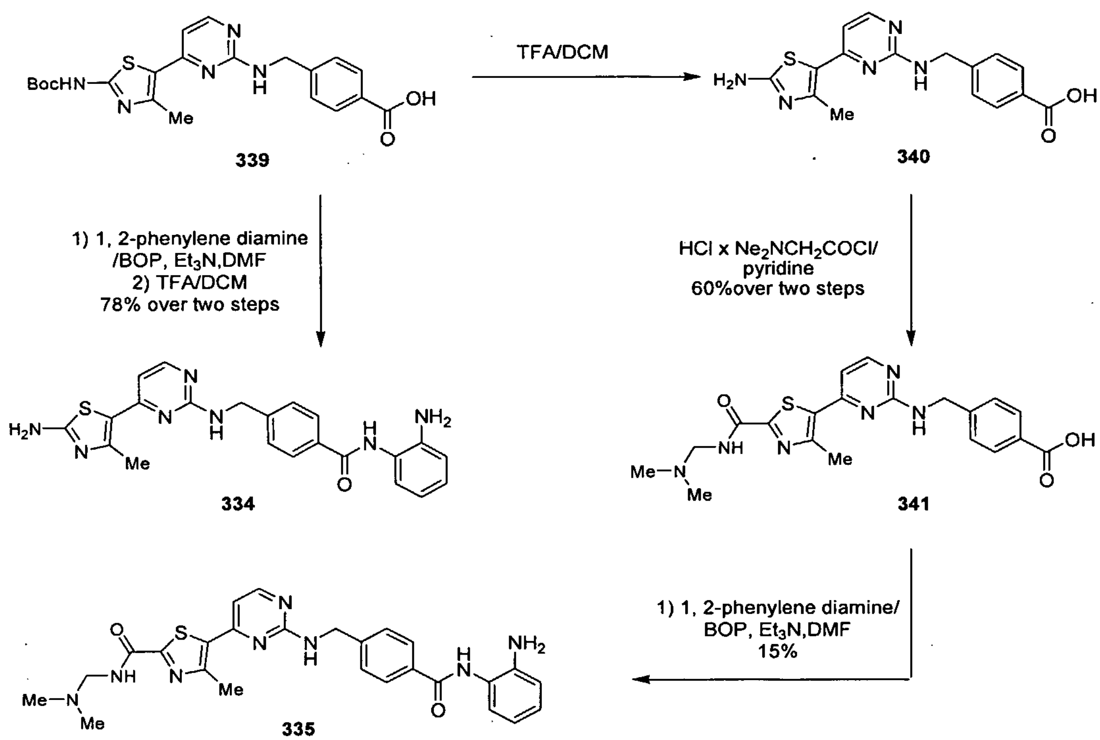
[0800] Title compound was obtained according to the procedure described for the synthesis of compound **26a** (scheme 6, step 4, coupling with 1,2-phenylene diamine) followed by the procedure described for the synthesis of the compound **117** (scheme 28, step 5, amino-group

deprotection). Yield 78% over two steps. Characterization of the title compound is provided in the Table 12.

[0801] Step 7. 4-((4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-ylamino)methyl)benzoic acid (340)

[0802] Title compound was obtained according to procedure described for the synthesis of the compound **117** (scheme 28, step 5, amino-group deprotection) in a quantitative yield (purity ca 90%). MS (m/z): 341.39 (calc) 342.1 (MH+) (found).

Scheme 64



[0803] Step 8. 4-((4-(2-((Dimethylamino)methylcarbamoyl)-4-methylthiazol-5-yl)pyrimidin-2-ylamino)methyl)benzoic acid (341)

[0804] Dimethylamino acetyl chloride hydrochloride (59.0 mg, 0.37 mmol) was added to a solution of the acid **340** (98.1 mg, 0.29 mmol) in pyridine (5 mL). The reaction mixture was stirred at room temperature for 1 day then another portion of dimethylaminoacetyl chloride hydrochloride (40 mg, 0.12 mmol) was added and the mixture was stirred at 40°C for another day. Pyridine was evaporated under reduced pressure and MeOH was added. A solid material was formed which was collected by filtration and purified by preparative RP HPLC (column AQUASIL C-18; 5 μM; 230 x 21.2 mm; eluent 20-80% MeOH in water) to afford 24,5 mg of the title compound (20% yield). MS (m/z): 426.49 (calc) 427.2 (MH+) (found).

[0805] Step 9. N-(2-aminophenyl)-4-((4-(5-(2-(dimethylamino)acetamido)-3-methylthiophen-2-yl)pyrimidin-2-ylamino)methyl)benzamide (335).

[0806] Title compound was obtained according to the procedure described for the synthesis of compound **26a** (scheme 6, step 4) in 15% yield (purified by preparative HPLC, column AQUASIL C-18; 5 µM; 230 x 21.2 mm; eluent 20-80% MeOH in water). Characterization of the title compound is provided in the Table 12.

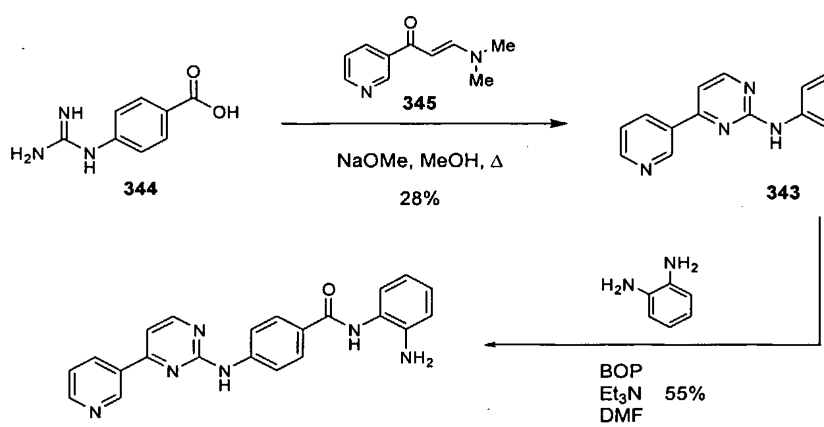
Example 188:

4-(4-(Pyridin-3-yl)pyrimidin-2-ylamino)-N-(2-aminophenyl)benzamide (342)

[0807] Step 1. 4-(4-(Pyridin-3-yl)pyrimidin-2-ylamino)benzoic acid (343)

[0808] Title compound was prepared according to the procedure described for the synthesis of compound **25a** (scheme 6, step3) replacing the guanindine **24** by 4-guanidinobenzoic acid (**344**) (Zlatoidsky P., Maliar T. *Eur. J. Med. Chem Chim. Ther.*; **1996**, *31*, 895-900) and (E)-3-(dimethylamino)-1-(pyrazin-2-yl)-prop-2-en-1-one (**23a**) by (E)-3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one (**345**) (Zimmermann J., Buchdunger E., et al. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1221-1226). Yield of the product 28%. MS (m/z): 292.29 (calc) 293.1 (MH+) (found).

Scheme 65

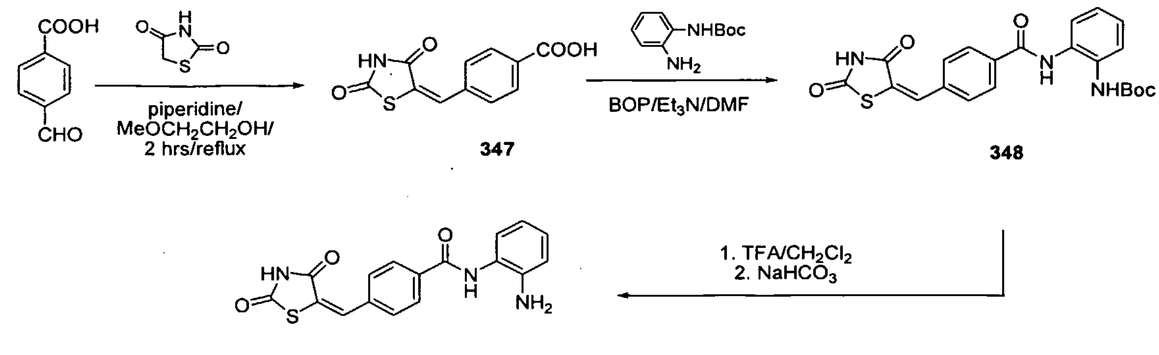


342: Example 188

[0809] Step 2. 4-(4-(Pyridin-3-yl)pyrimidin-2-ylamino)-N-(2-aminophenyl)benzamide (342).

[0810] Title compound was obtained in 54% yield according to the procedure described for the synthesis of compound **26a** (scheme 6, step 4) replacing acid **25a** by the acid **343**. Characterization of the title compound is provided in the Table 12.

Scheme 65a



346: Example 189

Example 189:

N-(2-Amino-phenyl)-4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzamide (346)

[0811] Step 1. 4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzoic acid (**347**)

[0812] A solution of 4-formyl-benzoic acid (1.0 g, 6.7 mmol), thiazolidine-2,4-dione (0.78 g, 6.7 mmol) and piperidine (1.32 ml, 13.3 mmol) in 2-methoxy-ethanol (20 ml) was refluxed for 2 hrs, cooled to the room temperature, evaporated and the oily residue was re-dissolved in water. Acidification of this solution with conc. HCl (pH 1-2) produced a precipitate which was collected by filtration, dried and triturated with hot acetone to afford the title compound (1.06 g, 64% yield). LRMS: 249.2 (calcd.), 248.1 $[M-H]^-$ (found).

[0813] Step 2. {2-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (**348**).

[0814] Following the procedure described for the synthesis of compound **115** (scheme 28) but substituting the acid **114** by the acid **347**, title compound was obtained in 63% yield. LRMS: 439.5 (calcd.), 462.4 $[M+Na]^+$ (found).

[0815] Step 3. N-(2-Amino-phenyl)-4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzamide (**346**)

[0816] Following the procedure described for the synthesis of compound 117 (scheme 28) but substituting the amide 116 by the amide 348, title compound was obtained in 37% yield. ^1H NMR: (400 MHz, DMSO-d_6, δ (ppm): 9.72 (s, 1H), 8.06 (d, j =8.2 Hz, 2H), 7.79 (s, 1H), 7.69 (d, J=8.4, 2H), 7.14 (d (dd) J=7.8, 1H), 6.95 (d (dd), J = 1.6 Hz, J=9.0, 1H), 6.75 (dd, J=1.2 Hz, J = 8.0 Hz, 1H), 6.56 (t (dd), J = 7.2 Hz 1H). LRMS: 339.4 (calcd.), 340.4 $[MH]^+$ (found).

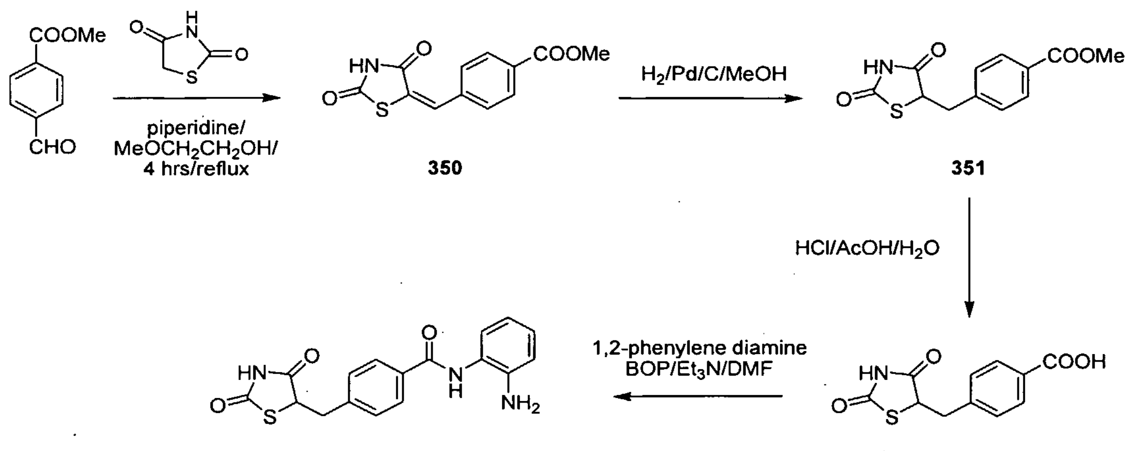
Example 190:

N-(2-Amino-phenyl)-4-(2,4-dioxo-thiazolidin-5-ylmethyl)-benzamide (349)

[0817] Step 1. 4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzoic acid methyl ester (**350**)

[0818] A solution of 4-formyl-benzoic acid methyl ester (1.0 g, 6.7 mmol), thiazolidine-2,4-dione (0.78 g, 6.7 mmol) and piperidine (0.66 ml, 6.7 mmol) in 2-methoxy-ethanol (20 ml) was refluxed for 2 hrs, cooled to the room temperature and evaporated. The residue was triturated with CH_2Cl_2 to produce a crystalline material which was collected by filtration to afford the title compound (620 mg, 35% yield). LRMS: 263.3 (calcd.), 264.1 $[MH]^+$ (found).

Scheme 66



[0819] Step 2. 4-(2,4-Dioxo-thiazolidin-5-ylmethyl)-benzoic acid methyl ester (**351**)

[0820] A solution of the methyl ester **350** (615 mg, 2.32 mmol) in MeOH (120 ml) was hydrogenated over 10% Pd/C (615 mg, Degussa type) for 2 hours at room temperature. Another portion of Pd/C (300 mg) was added and the hydrogenation proceeded for another 3 hrs (monitored by MS). The reaction mixture was filtered through a celite pad, evaporated and the residue was purified by flash chromatography, eluent EtOAc-CH_2Cl_2 (1:2), to produce the title compound (570 mg, 92% yield). LRMS: 265.3 (calcd.), 266.1 $[MH]^+$ (found).

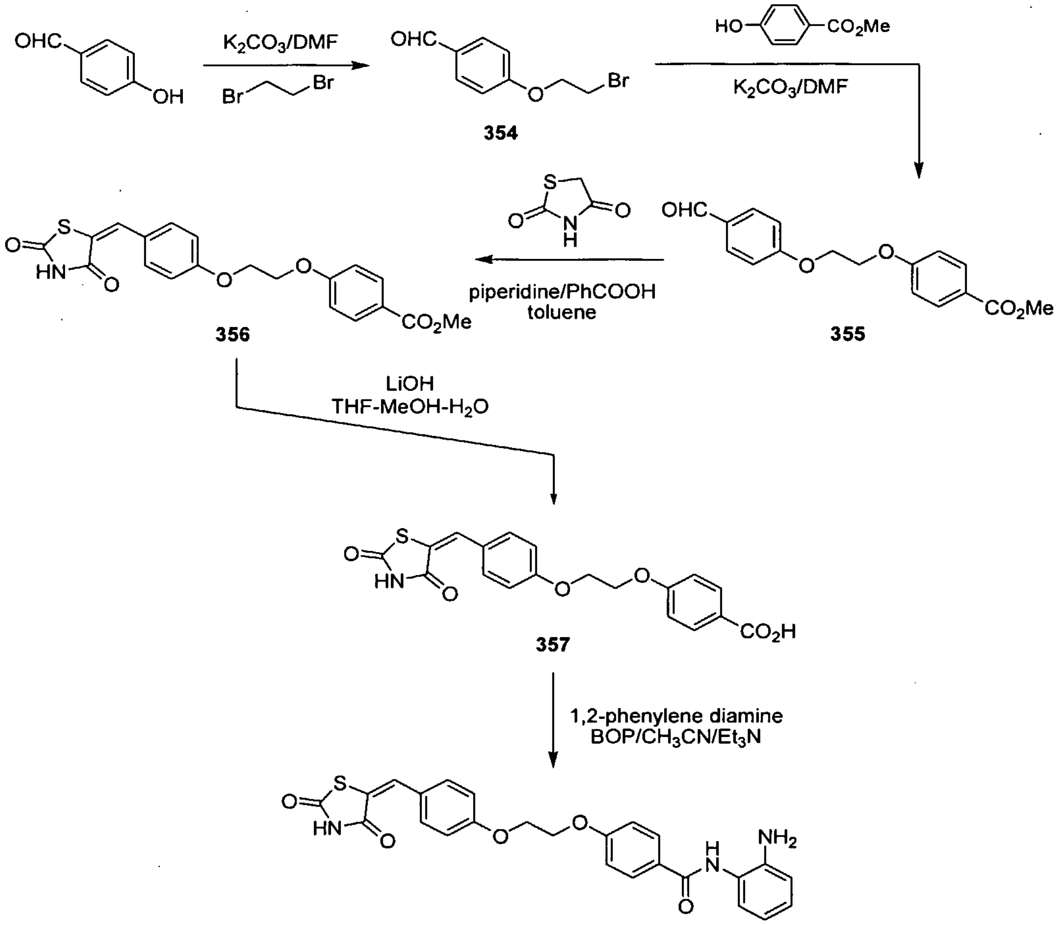
[0821] Step 3. 4-(2,4-Dioxo-thiazolidin-5-ylmethyl)-benzoic acid (**352**)

[0822] A solution of methyl ester **351** (250 mg, 0.94 mmol) in AcOH (10 ml) was treated with conc. HCl (5 ml) and the reaction mixture was heated at 120°C for 2 hrs, cooled and evaporated to produce a solid residue which was re-suspended in water and collected by filtration to afford the title compound (98 mg, 41% yield). LRMS: 251.3 (calcd.), 250.1 $[M\text{-}H]^-$ (found).

[0823] Step 4. N-(2-Amino-phenyl)-4-(2,4-dioxo-thiazolidin-5-ylmethyl)-benzamide (**349**)

[0824] Following the procedure described for the synthesis of compound **10a** (scheme 2, Example 2) but replacing acid **9** by the acid **352**, title compound was obtained in 51% yield. ^{1}H NMR: (400 MHz, DMSO-d$_6$, δ (ppm): 12.04 (br s, 1H), 9.62 (s, 1H), 7.90 (d, j =8.2 Hz, 2H), 7.36 (d, J=8.2, 2H), 7.16 (d (dd) J=8.4, 1H), 7.13 (d (dd), J=6.7, 1H), 6.95 (dd, J=1.6 Hz, J = 7.8 Hz, 1H), 6.75 (dd, j = 1.4 Hz, j = 8.0 Hz, 1H), 6.57 (dd, j = 1.4 Hz, 7.6 Hz, 1H), 4.99 (dd, J = 4.7 Hz, J = 9.0 Hz, 1H), 4.96 (br s, 2H), 3.45 (dd, J = 4.5 Hz, J = 14.1 Hz, 1H), 3.22 (dd, J = 9.0 Hz, J = 14.3 Hz, 1H). LRMS: 341.3 (calcd.), 342.3 [MH]$^+$ (found).

<u>Scheme 67</u>



<u>Example 191:</u>

(E)-N-(2-aminophenyl)-4-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)ethoxy)benzamide (353)

[0825] Step 1: 4-(2-bromoethoxy)benzaldehyde (**354**)

[0826] To a suspention of K_2CO_3 (4.52 g, 32.7 mmol), 1,2-dibromoethane (10.6 ml, 122.8 mmol) in DMF (12 mL) was added a solution of 4-hydroxybenzaldehyde (1.0 g, 8.2 mmol) in DMF (3 mL) at 0°C. The mixture was stirred at room temperature for 18 h., filtered and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc-hexane (increasing percentage of EtOAc from 20 to 25%) to afford the title compound (1.21 g, 64% yield). ^{1}H NMR: ($CDCl_3$) δ (ppm): 9.88 (s, 1H), 7.84 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.0 Hz, 2H), 4.38 (t, J=6 Hz, 2H), 3.67 (t, J=6 Hz, 2H). LRMS (ESI): (calc.) 227.9, 229.9; (found) 229.1, 231.3 $(MH)^+$.

[0827] Step 2: Methyl 4-(2-(4-formylphenoxy)ethoxy)benzoate (**355**)

[0828] To a solution of **354** (1.21 g, 5.27 mmol) in DMF (10 mL) was added methyl 4-hydroxybenzoate (0.80 g, 5.27 mmol) and K_2CO_3 (2.91 g, 21.1 mmol). The resultant mixture was stirred at 60°C for 6 h, filtered, and evaporated. The residue was purified by silica gel column chromatography, eluent EtOAc-hexane (1:2) to afford title compound (0.83 g, 53%). LRMS (ESI): (calc.) 300.3; (found) 301.4 $(MH)^+$.

[0829] Step 3: (E)-Methyl 4-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)ethoxy)benzoate (**356**)

[0830] To a solution of **355** (1.59 g, 3.86 mmol) in toluene (10 mL) was added thiazolidine-2,4-dione (542 mg, 4.63 mmol), benzoic acid (61.3 mg, 0.50 mmol) and piperidine (57 uL, 0.58 mmol). The resultant mixture was refluxed with the Dean-Stark adapter for 1/2 h and cooled to the room temperature. A precipitate formed which was collected by filtration to afford the title compound (1.41 g, 92%). ^{1}H NMR: (DMSO-d_6) δ (ppm): 7.90 (d, J=8.8 Hz, 2H), 7.73 (s, 1H), 7.54 (d, J= 8.8 Hz, 2H), 7.14 (d, J=8.8 Hz, 2H), 7.08 (d J=8.8 Hz, 2H), 4.42 (bs, 4H), 3.80 (s, 3H). LRMS (ESI): (calc.) 399.1; (found) 400.0 $(MH)^+$.

[0831] Step 4: (E)-4-(2-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenoxy)ethoxy)benzoic acid (compound **357**)

[0832] To a solution of methyl ester **356** (647mg, 1.62 mmol) in THF (15 mL) was added methanol (2 mL), water (2 mL) and lithium hydroxide monohydrate (340 mg, 8.11 mmol). The mixture was heated at 60°C for 1 hour, acidified with 10% HCl solution and extracted with ethyl acetate. The organic extract was dried over $MgSO_4$, filtered, and evaporated to afford the title compound (141 mg, 22%). ^{1}H NMR: (MeOD-d_4) δ (ppm): 7.97 (d, J=8.8 Hz, 2H), 7.75 (s, 1H), 7.53 (d, J=8.8 Hz , 2H), 7.12 (d, J=8.8 Hz, 2H), 7.04 (d, J=8.8 Hz, 2H), 4.44 (4H, bs). LRMS (ESI): (calc.) 385.4; (found) 392.3 $(MLi)^+$.

[0833] Step 5: (E)-N-(2-Aminophenyl)-4-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)ethoxy)benzamide (**353**)

[0834] Acid **357** (141 mg, 0.37 mmol), benzene-1,2-diamine (40 mg, 0.37 mmol) and BOP (161 mg, 0.37 mmol) were dissolved in CH_3CN (5 mL). Triethylamine (0.73 mmol, 203 μL) was added and the reaction was stirred for 18 hours at room temperature. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography with gradient elution by EtOAc-hexane mixture (increasing percentage of EtOAc from 33 to 100%) to afford the title compound (34.2 mg, 19%). ^{1}H NMR: (DMSO-d_6) δ (ppm): 10.00 (s,1H), 8.44 (s,1H), 7.96 (s,1H), 7.57-7.65 (m,3H), 7.49 (t, J = 7.6 Hz, 2H), 7.36-7.43 (m,2H), 7.31-7.35 (m,1H), 4.59 (s,2H), 4.23 (s,2H), 3.74 (s,3H), 3.11-3.20 (m,2H), 2.37 (t, J = 7.2 Hz, 2H), 1.60-1.71 (m,2H), 1.45-1.55 (m,2H), 1.32-1.43 (m,2H). LRMS (ESI): (calc.) 460.5; (found) 461.3 $(MH)^+$.

Example 192:

N-(2-Aminophenyl)-4-(2-(4-((2,4-dioxothiazolidin-5-yl)methyl)phenoxy)ethoxy)benzamide (358)

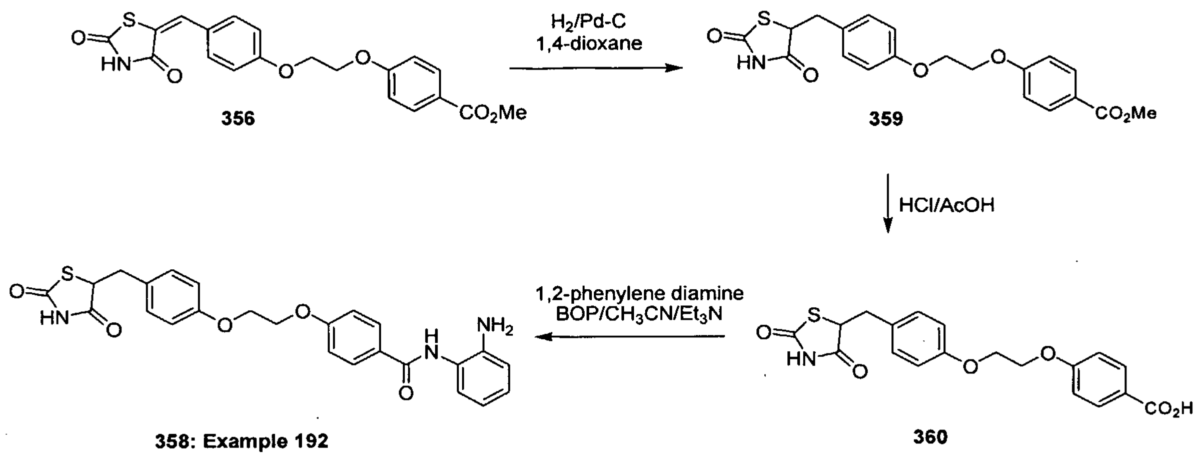
[0835] Step 1: Methyl 4-(2-(4-((2,4-dioxothiazolidin-5-yl)methyl)phenoxy)ethoxy)benzoate (**359**)

[0836] To a solution of **356** (scheme 67) (672 mg, 1.68 mmol) in 1,4-dioxane (10 mL) was added 10% Pd/C (2.3g, 2.18 mmol). The resultant mixture was stirred under hydrogen atmosphere for 2 days at room temperature, filtered through a celite pad and concentrated under reduced pressure to afford **359** (379 mg, 56%). LRMS (ESI): (calc.) 401.4; (found) 424.2 $(M+Na)^+$. ^{1}H NMR: ($CDCl_3$) δ (ppm): 8.15 (bs, 1H), 7.99 (d, J=8.8 Hz, 2H), 7.16 (d, J=8.8 Hz, 2H), 6.96 (d, J=8.8 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 4.52 (dd, J=9.2 , 4.0 Hz, 1H), 4.38-4.37 (m, 2H), 4.32-4.32 (m, 2H), 3.89 (s, 3H), 3.45 (dd, J=14.1, 4.0 Hz, 1H), 3.14 (dd, J=14.0, 9.2 Hz, 1H).

[0837] Step 2: 4-(2-(4-((2,4-Dioxothiazolidin-5-yl)methyl)phenoxy)ethoxy)benzoic acid (**360**)

[0838] To a solution of methyl ester **359** (872 mg, 2.17 mmol) in glacial AcOH (30 mL) was added conc. HCl (10 mL). The mixture was heated at 120°C for 3 hours. The solvents were remove under reduced pressure to afford the title compound (833 mg, 99%). ^{1}H NMR: (DMSO-d_6) δ (ppm): 12.61 (bs, 1H), 12.01 (s, 1H), 7.91 (d, J=8.8 Hz, 2H), 7.19 (d, J=8.8 Hz, 2H), 7.08 (d, J=8.8 Hz, 2H), 6.95 (d, J=8.8 Hz, 2H), 4.91 (dd, J=9.2, 4.4 Hz, 1H), 4.40-4.42 (m, 2H), 4.33-4.36 (m, 2H), 3.32 (d, J=4.0 Hz, 1H), 3.10 (dd, J=14.0, 9.6 Hz, 1H). LRMS (ESI): (calc.) 387.4; (found) 386.2 $(M-H)^-$.

Scheme 68



[0839] Step 3: N-(2-aminophenyl)-4-(2-(4-((2,4-dioxothiazolidin-5-yl)methyl)phenoxy)ethoxy)benzamide (**358**)

[0840] Following the same procedure as described for compound **393** (step 5, scheme 67, example 191) but substituting acid **357** for the acid **360** title compound was obtained as a beige solid (57 mg, 33% yield). ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.34 (s, 1H), 7.74-7.78 (m, 3H), 6.93-6.98 (m,3H), 6.88 (d J=8.8 Hz, 2H), 6.73-6.78 (m, 3H), 6.57 (dd, J=8.0, 1.2 Hz, 1H), 6.38 (dt, J=8.0, 1.2 Hz, 1H), 4.68 (dd, J=8.8, 4.4 Hz, 2H), 4.19-4.21 (m, 2H), 3.11 (d, J=4.4 Hz, 1H), 2.88 (dd, J=14.0, 9.2 Hz, 1H). LRMS (ESI): (calc.) 477.4; (found) 478.4 $(MH)^+$.

Scheme 69

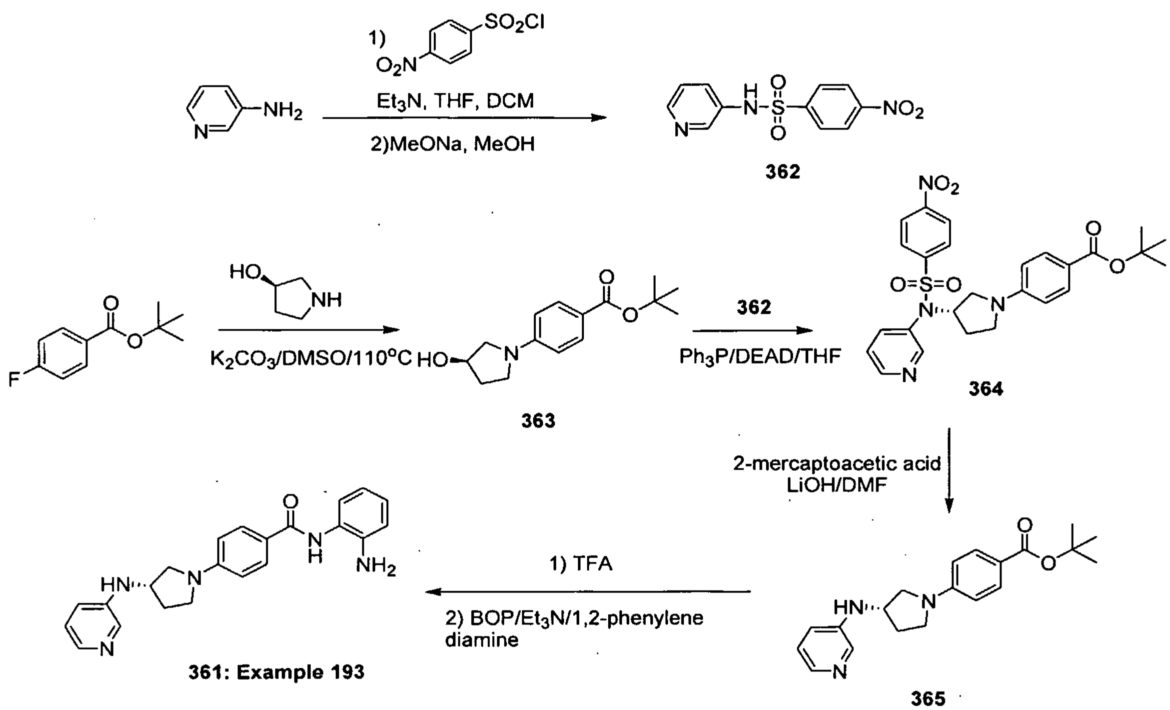
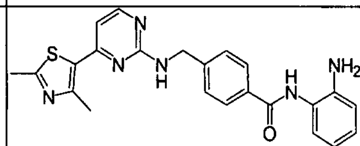
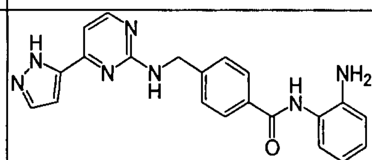
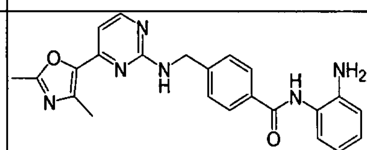
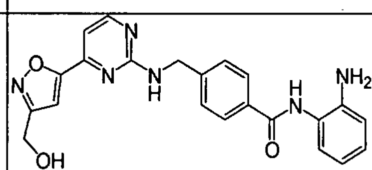
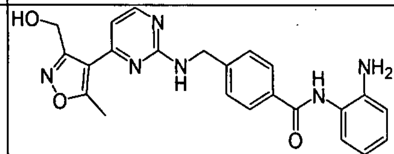
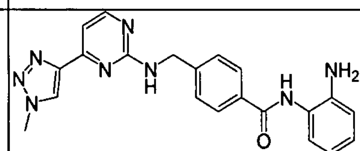
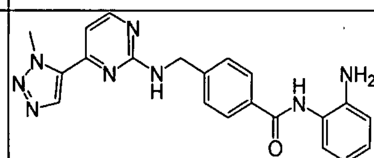
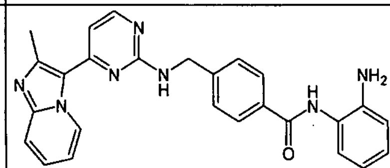
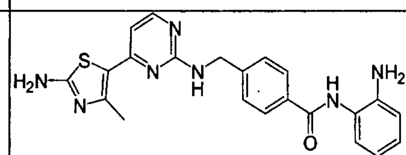
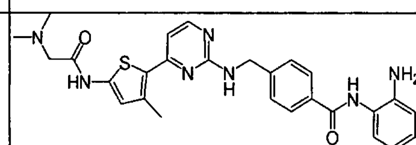
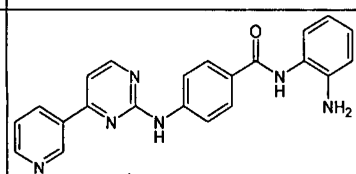

1)
SO2Cl
O2N
NH2
N
Et3N, THF, DCM
2)MeONa, MeOH
H
N-S-
O
NO2
362
HO
NH
F
O
K2CO3/DMSO/110°C
HO
N
363
Ph3P/DEAD/THF
O=S=O
364
2-mercaptoacetic acid
LiOH/DMF
HN
365
1) TFA
2) BOP/Et3N/1,2-phenylene diamine
H
361: Example 193

Table 12. Characterization of examples 178 – 188.

Ex	Cpd	Structure	Name	Characterization	Scheme
178	314		N-(2-aminophenyl)-4-((4-(2,4-dimethylthiazol-5-yl)pyrimidin-2-ylamino)methyl)benzamide	^{1}H NMR (DMSO-d$_6$) δ (ppm): 9.56 (s, 1H), 8.30 (d, J=5.1 Hz, 1H), 7.92 (s, 1H), 7.89 (d, J=8.2 Hz, 2H), 7.43 (d, J=7.4 Hz, 2H), 7.12 (d, J=7.6 Hz, 1H), 6.94 (td, J=7.8, 1.4 Hz, 1H), 6.82 (d, J=5.1 Hz, 1H), 6.75 (dd, J=8.0, 1.4 Hz, 1H), 6.57 (td, J=7.6, 1.4 Hz, 1H), 4.87 (s, 2H), 4.56 (d, J=6.3 Hz, 2H), 2.61 (s, 3H), 2.56 (s, 3H).MS (m/z): 430.53 (calc) 431.1 (MH+) (found)	6
179	315		4-((4-(1H-pyrazol-5-yl)pyrimidin-2-ylamino)methyl)-N-(2-aminophenyl)benzamide	^{1}H NMR (DMSO-d$_6$) δ (ppm): 13.16 (s, 1H), 9.56 (s, 1H), 8.26 (s, 1H), 7.89 (d, J=8.2 Hz, 2H), 7.80 (d, J=14.5 Hz, 2H), 7.47 (s, 2H), 7.13 (d, J=7.6 Hz, 1H), 7.08 (s, 0.5H), 6.94 (td, J=7.2, 1.6 Hz, 1H), 6.80 (s, 0.5H), 6.74 (dd, J=7.9, 1.6 Hz, 1H), 6.56 (td, J=6.9, 1.4 Hz, 1H), 4.86 (s, 2H), 4.60 (s, 2H).MS (m/z): 385.42 (calc) 386.2 (MH+) (found)	6
180	316		N-(2-aminophenyl)-4-((4-(2,4-dimethyloxazol-5-yl)pyrimidin-2-ylamino)methyl)benzamide	^{1}H NMR (DMSO-d$_6$) δ (ppm): 9.57 (s, 1H), 8.31 (d, J=4.5 Hz, 1H), 7.93-7.89 (m, 3H), 7.41 (d, J=8.2 Hz, 2H), 7.12 (d, J=7.6 Hz, 1H), 6.94 (td, J=7.2, 1.6 Hz, 1H), 6.76-6.73 (m, 2H), 6.56 (td, J=8.0, 1.2 Hz, 1H), 4.87 (s, 2H), 4.59 (d, J=6.5 Hz, 2H), 2.44 (s, 3H), 2.35 (s, 3H).MS (m/z): 414.46 (calc) 415.3 (MH+) (found)	6
181	317		N-(2-aminophenyl)-4-((4-(3-(hydroxymethyl)isoxazol-5-yl)pyrimidin-2-ylamino)methyl)benzamide	^{1}H NMR (MeOD-d$_4$) δ (ppm): 8.42 (d, J=5.1 Hz, 1H), 7.92 (d, J=8.0 Hz, 2H), 7.53 (d, J=8.8 Hz, 2H), 7.16 (d, J=8.4 Hz, 1H), 7.08 (d, J=4.9 Hz, 1H), 7.06-7.04 (m, 2H), 6.89 (d, J=8.0 Hz, 1H), 6.75 (t, J=7.6 Hz, 1H), 4.72 (s, 2H), 4.69 (s, 2H).MS (m/z): 416.43 (calc) 417.3 (MH+) (found)	59, 6

Ex	Cpd	Structure	Name	Characterization	Scheme
182	**321**		N-(2-aminophenyl)-4-((4-(3-(hydroxymethyl)-5-methylisoxazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide	^{1}H NMR (DMSO-d_6) δ (ppm): 9.54 (s, 1H), 8.34 (d, J=5.1 Hz, 1H), 7.94-7.88 (m, 3H), 7.42 (d, J=8.0 Hz, 2H), 7.13 (d, J=7.6 Hz, 1H), 6.94 (t, J=7.0 Hz, 2H), 6.75 (d, J=7.8 Hz, 1H), 6.57 (t, J=7.4 Hz, 1H), 5.53 (t, J=5.9 Hz, 1H), 4.87 (s, 2H), 4.65-4.59 (m, 4H). (CH_3 singlet is probably overlapped by DMSO signal)^{1}H NMR (MeOD-d_4) δ (ppm): 8.32 (d, J=5.3 Hz, 1H), 7.92 (d, J=8.2 Hz, 2H), 7.48 (d, J=8.2 Hz, 2H), 7.16 (d, J=7.6 Hz, 1H), 7.06 (t, J=7.2 Hz, 1H), 6.94 (d, J=5.3 Hz, 1H), 6.88 (d, J=8.2 Hz, 1H), 6.76 (t, J=6.3 Hz, 1H), 4.72 (s, 2H), 4.70 (s, 2H), 2.61 (s, 3H).MS (m/z): 430.46 (calc) 431.2 (MH+) (found)	60, 6
183	**325**		N-(2-aminophenyl)-4-((4-(1-methyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide	^{1}H NMR (DMSO-d_6) δ (ppm): 9.56 (s, 1H), 8.33 (d, J=4.9 Hz, 1H), 8.20 (s, 1H), 7.96 (t, J=6.3 Hz, 1H), 7.89 (d, J=8.2 Hz, 2H), 7.47 (s, 2H), 7.12 (d, J=7.8 Hz, 1H), 7.02 (d, J=4.7 Hz, 1H), 6.94 (td, J=7.2, 1.5 Hz, 1H), 6.75 (dd, J=7.9, 1.3 Hz, 1H), 6.57 (td, J=7.9, 1.4 Hz, 1H), 4.86 (s, 2H), 4.60 (d, J=6.3 Hz, 2H), 4.22 (s, 3H).MS (m/z): 400.44 (calc) 401.2 (MH+) (found)	61
184	**326**		N-(2-aminophenyl)-4-((4-(3-methyl-3H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide	^{1}H NMR (DMSO-d_6) δ (ppm): 9.57 (s, 1H), 8.42 (s, 1H), 8.35 (s, 1H), 8.14 (s, 1H), 7.90 (d, J=8.2 Hz, 2H), 7.43 (d, J=8.2 Hz, 2H), 7.13 (d, J=7.2 Hz, 1H), 7.08 (d, J=5.1 Hz, 1H), 6.94 (td, J=8.2, 1.6 Hz, 1H), 6.75 (dd, J=7.8, 1.2 Hz, 1H), 6.57 (t, J=8.2 Hz, 1H), 4.87 (s, 2H), 4.62 (d, J=6.3 Hz, 2H), 4.40 (s, 1H), 4.12 (s, 2H).MS (m/z): 400.44 (calc) 401.2 (MH+) (found)	61

Ex	Cpd	Structure	Name	Characterization	Scheme
185	332		N-(2-aminophenyl)-4-((4-(2-methylH-imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-ylamino)methyl)benzamide	^{1}H-NMR, DMSO-d6 δ(ppm): 9.60 (s, 1H); 8.97 (bs, 1H); 8.35 (bs, 1H); 8.03 (t, J=6.3 Hz, 1H); 7.94 (d, J=8.2 Hz, 2H); 7.56 (bs, 1H); 7.47 (d, J=8.2 Hz, 2H); 7.33 (bs, 1H); 7.13 (d, J=7.3 Hz, 1H); 6.94 (dt, J= 1.4, 7.3 Hz, 1H); 6.85 (d, J=4.3 Hz, 1H); 6.75 (dd, J= 1.0, 8.0 Hz, 1H); 6.71 (bs, 1H); 6.57 (t, J=7.3 Hz, 1H); 4.87 (bs, 2H); 4.62 (d, J= 6.1 Hz, 2H); 2.59 (bs, 3H). MS (m/z): 449.51 (calc) 450.2 (MH+) (found)	62, 6
186	334		4-((4-(2-amino-4-methylthiazol-5-yl)pyrimidin-2-ylamino)methyl)-N-(2-aminophenyl)benzamide	^{1}H NMR (MeOD-d_4) δ (ppm): 8.16 (d, J=5.9 Hz, 1H), 8.00 (d, J=8.2 Hz, 2H), 7.54 (d, J=8.0 Hz, 2H), 7.35-7.26 (m, 4H), 6.92 (d, J=6.1 Hz, 1H), 4.73 (s, 2H), 2.55 (s, 3H).MS (m/z): 431.51 (calc) 432.2 (MH+) (found)	63
187	335		N-(2-aminophenyl)-4-((4-(5-(2-(dimethylamino)acetamido)-3-methylthiophen-2-yl)pyrimidin-2-ylamino)methyl)benzamide	^{1}H NMR (MeOD-d_4) δ (ppm): 8.23 (d, J=5.3 Hz, 1H), 7.92 (d, J=8.0 Hz, 2H), 7.54 (d, J=8.0 Hz, 2H), 7.16 (d, J=7.4 Hz, 1H), 7.06 (t, J=7.2 Hz, 1H), 6.89-6.86 (m, 2H), 6.75 (t, J=7.6 Hz, 1H), 4.68 (s, 2H), 3.60 (s, 2H), 2.59 (s, 6H), 2.56 (s, 3H).MS (m/z): 516.62 (calc) 517.3 (MH+) (found)	63
188	342		N-(2-aminophenyl)-4-(4-(pyridin-3-yl)pyrimidin-2-ylamino)benzamide	^{1}H NMR (DMSO-d_6) δ (ppm): 10.10 (s, 1H), 9.52 (s, 1H), 9.35 (d, J=1.9 Hz, 1H), 8.73 (dd, J=4.9, 1.8 Hz, 1H), 8.66 (d, J=5.1 Hz, 1H), 8.52 (dt, J=8.2, 2.2 Hz, 1H), 7.96 (d, J=2.0 Hz, 4H), 7.61 (d, J=4.9 Hz, 1H), 7.59 (d, J=5.1 Hz, 1H), 7.15 (d, J=7.3 Hz, 1H), 6.95 (td, J=8.0, 1.6 Hz, 1H), 6.77 (dd, J=7.8, 1.2 Hz, 1H), 6.59 (td, J=7.4, 1.4 Hz, 1H), 4.89 (s, 2H).MS (m/z): 382.42 (calc) 383.3 (MH+) (found)	64

Example 193:

(S)-*N*-(2-Aminophenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide (361)

[0841] Step 1: N-p-Nosyl-3-pyridine (362):

[0842] To a stirred solution of 2-aminopyridine (3.03 g, 32.2 mmol) in THF (15mL) were successively added DCM (30 mL), 4-nitrobenzenesulfonyl chloride (1.50g, 68.7mmol), and Et_3N (9.88mL, 70.9mmol). The solution turned orange and a precipitate formed. The suspension was allowed to stir at room temperature for 1h, solvents were evaporated under reduced pressure and the solid residue was suspended in methanol (200 mL). To the suspension a large excess (>10 eq) of sodium methoxide was added, the mixture was stirred at 50°C for 3 h, quenched with HCl 1N (2mL) and concentrated under reduced pressuré at 80°C until the volume became ~ 50mL. The concentrated solution was further acidified with 1N HCl until neutral pH. A precipitate formed which was collected by filtration to afford the title compound (7.67 g, 85% yield). ^{1}H NMR (DMSO-d_6) δ (ppm): 10.88 (s, 1H), 8.36 (d, J=9.0 Hz, 2H), 8.28 (dd, J=6.1, 1.4 Hz, 1H), 8.27 (d, J=2.5 Hz, 1H), 7.50 (ddd, J=8.4, 2.7, 1.6 Hz, 1H), 7.30 (ddd, J=8.2, 4.7, 0.8 Hz, 1H). m/z: 280.1 (MH^+).

[0843] Step 2: tert-Butyl 4-((R)-3-hydroxypyrrolidin-1-yl)benzoate (363):

[0844] To a solution of *t*-butyl 4-fluorobenzoate (2.17g, 11.0 mmol) and (R)-(+)-3-pyrrolidinol (1.00g, 11.5 mmol) in DMSO (8 mL) was added potassium carbonate (1.53g, 11.0 mmol). The mixture was stirred at 130°C for 18h and poured into stirring water (100mL) while still hot. The resulting beige precipitate was collected by filtration and dried at 120°C for 1.5h to afford the title compound (2.64g, 91% yield). ^{1}H NMR (Acetone-d_6) δ (ppm): 7.78 (d, J=9.0 Hz, 2H), 6.54 (d, J=8.8 Hz, 2H), 4.58 (bs, 1H), 4.15 (bs, 1H), 3.55 (dd, J=10.36, 4.7 Hz, 1H), 3.49 (t, J=6.8 Hz, 1H), 3.42 (td, J=9.2, 2.3 Hz, 1H), 3.28 (d, J=10.8 Hz, 1H), 2.21-2.10 (m, 1H), 2.09-2.03 (m, 1H), 1.56 (s, 9H).m/z: 520.3 (MH^+).

[0845] Step 3: tert-Butyl 4-((S)-3-N-p-nosyl (pyridin-3-ylamino)pyrrolidin-1-yl)benzoate (364)

[0846] To a solution of compound **362** (6.00g, 21.5 mmol) in THF (100 mL), were successively added carbinol **363** (5.66g, 21.5 mmol), triphenylphosphine (6.76g, 25.8 mmol) and diethyl azodicarboxylate (4.06mL, 25.8 mmol). The mixture was stirred at room temperature for 18h and the solvent was removed *in vacuo*. The residue was purified by flash chromatography using EtOAc/Hex (40:60) as an eluent to afford the title compound (4.68g, 42% yield). ^{1}H NMR (DMSO-d_6) d(ppm): 8.58 (dd, J=4.7, 1.4 Hz, 1H), 8.48 (d, J=8.0 Hz, 2H), 8.38 (d, J=2.0 Hz, 1H), 8.13 (d, J=9.0, 2H), 7.72 (d, J=9.0 Hz, 2H), 7.61 (ddd, J=8.0, 2.5, 1.6 Hz, 1H), 7.39 (dd, J=8.2, 4.9 Hz, 1H), 6.43 (d, J=9.0 Hz, 2H), 5.17 (quint, J=8.2 Hz, 1H), 3.77 (dd, J=10.4, 7.2

Hz, 1H), 3.36 (dd, J=10.4, 6.7 Hz, 1H), 3.26 (dd, J=15.1, 7.8 Hz, 1H), 3.06 (td, J=12.3, 3.3 Hz, 1H), 2.43-2.38 (m, 1H), 2.02-1.94 (m, 1H), 1.55 (s, 9H). m/z: 525.3 (MH^+).

[0847] Step 4: tert-Butyl 4-((S)-3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzoate (365)

[0848] To a solution of the nitro compound **364** (4.68g, 8.92 mmol) in DMF (45mL), were successively added lithium hydroxide (1.31g, 31.2 mmol) and thioglycolic acid (930µL, 13.4 mmol). The mixture was stirred for 3 days at room temperature, the solvent was removed *in vacuo* at 80°C and the residue was partitioned between EtOAc and H_2O. Organic layer was collected and extracted with HCl 1N. Acidic layer was collected and neutralized with a saturated $NaHCO_3$ solution. A white precipitate was formed which was extracted with EtOAc. The EtOAc solution was washed with brine, dried over MgSO4, and concentrated *in vacuo* to afford the title compound (1.65g, 54%yield) as a white solid. ^{1}H NMR: (Acetone-d_6) δ(ppm): 8.08 (d, J=2.2 Hz, 1H), 7.86 (d, J=4.3 Hz, 1H), 7.79 (d, J=9.0 Hz, 2H), 7.09 (dd, J= 8.2, 4.3 Hz, 1H), 7.05 (ddd, J=8.2, 2.7, 1.6 Hz, 1H), 6.57 (d, J= 8.8 Hz, 2H), 5.54 (d, J=6.5 Hz, 1H), 4.32 (sext, J=5.3 Hz, 1H), 3.78 (dd, J=10.2, 5.9 Hz, 1H), 3.56 (dd, J=17.0, 7.2 Hz, 1H), 3.47 (td, J=8.0, 5.1 Hz, 1H), 3.31 (dd, J=10.2, 3.9 Hz, 1H), 2.44 (sext., J=7.8 Hz, 1H), 2.13 (sext, J=5.1 Hz, 1H), 1.56 (s, 9H). m/z: 340.3 (MH^+).

[0849] Step 5. (S)-N-(2-Aminophenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide (361)

[0850] To a suspension of compound **365** (19mg, 0.56 mmol) in DCM 500µL was added trifluoroacetic acid (200µL). The solution was refluxed at 50°C for 3h and concentrated *in vacuo* to produce a white solid. This material was dissolved in DMF (500µL) and was treated with Et_3N (16µL, 0.118 mmol) and BOP (30mg, 0.067 mmol). The reaction mixture was stirred for 10 min. and 1,2-henylenediamine (7mg, 0.061 mmol) and another portion of Et_3N (23µL, 0.168 mmol) were added. The mixture was stirred for 2h at room temperature and DMF was removed *in vacuo* at 80°C. The residue was partitioned between EtOAc and H_2O. The organic layer was collected and extracted with 1N HCl and neutralized with sat. $NaHCO_3$. A precipitate formed which was extracted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography using MeOH/$CHCl_3$ (7:93) as the eluent to afford the title compound (11 mg, 52% yield). ^{1}H NMR: (CD_3OD) δ(ppm): 7.97 (d, J=2.7 Hz, 1H), 7.86 (d, J=8.8 Hz, 2H), 7.78 (dd, J=4.7, 1.0 Hz, 1H), 7.18-7.10 (m, 3H), 7.05 (td, J=7.4, 0.6 Hz, 1H), 6.89 (dd, J=7.8, 1.2 Hz, 1H), 6.76 (td, J=7.4, 1.4 Hz, 1H), 6.64 (d, J=8.8 Hz, 2H), 4.25 (quint, J=4.9 Hz, 1H), 3.77 (dd, J=10.2, 6.1 Hz, 1H), 3.57 (dd, J=17.0, 7.0 Hz, 1H), 3.49 (td, J=8.0, 5.3 Hz, 1H), 3.29 (q, J=6.7Hz, 1H), 2.41 (sext, J=7.2 Hz, 1H), 2.10 (sext, J=4.9 Hz, 1H). m/z: 372.4 (MH^+).

Example 194:

(R)-*N*-(2-Aminophenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide (366)

[0851] The title compound was obtained following the same procedures described in scheme 69, example 193 but substituting (R)-(+)-3-pyrrolidinol for (S)-(-)-3-pyrrolidinol. (108mg, 21% yield) ^{1}H NMR: (DMSO-d_6) δ(ppm): 9.34 (s, 1H), 8.00 (d, J=2.3 Hz, 1H), 7.84 (d, J=8.8 Hz, 2H), 7.77 (dd, J=4.7, 1.2 Hz, 1H), 7.12 (d, J=7.6 Hz, 1H), 7.08 (dd, J=8.0, 4.5 Hz, 1H), 6.99-6.97 (m, 1H), 6.92 (t, J=7.8 Hz, 1H), 6.75 (d, J=7.8 Hz, 1H), 6.60-6.56 (m, 3H), 6.17 (d, J=6.8 Hz, 1H), 4.81 (s, 2H), 4.19-4.17 (m, 1H), 3.71 (dd, J=10.2, 6.5 Hz, 1H), 3.53-3.47 (m, 1H), 3.42-3.38 (m, 1H), 3.18 (dd, J=10.4, 4.1 Hz, 1H), 2.32 (sext, J=6.3 Hz, 1H), 1.99 (sext, J=4.7 Hz, 1H). m/z: 374.2 (MH$^+$).

Example 195:

(S)-N-(2-Aminophenyl)-4-(3-(pyridin-3-yloxy)pyrrolidin-1-yl)benzamide (367)

[0852] The title compound was obtained following the same procedures described in scheme 69, example 193 but skipping steps 1 and 4 and substituting compound **362** for 3-hydroxypyridine (24mg, 44% yield) ^{1}H NMR: (Acetone-d_6) δ(ppm): 8.88 (s, 1H), 8.31 (d, J=2.9 Hz, 1H), 8.19 (d, J=4.7 Hz, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.41 (ddd, J=8.4, 2.9, 1.4 Hz, 1H), 7.31 (ddd, J=8.4, 4.5, 0.6 Hz, 1H), 7.26 (d, J=7.8 Hz, 1H), 6.97 (td, J=7.8, 1.4 Hz, 1H), 6.85 (dd, J=8.0, 1.4 Hz, 1H), 6.66 (d, J=9.0 Hz, 2H), 6.65 (td, J=8.0, 1.4 Hz, 1H), 5.34-5.32 (m, 1H), 4.62 (s, 2H), 3.84 (dd, J=11.3, 4.7 Hz, 1H), 3.61-3.56 (m, 3H), 2.50-2.34 (m, 2H). m/z: 375.2 (MH$^+$).

Example 196:

(R)-N-(2-Aminophenyl)-4-(3-(pyridin-3-yloxy)pyrrolidin-1-yl)benzamide (368)

[0853] The title compound was obtained following the same procedures described in scheme 69, example 193 skipping steps 1 and 4 and substituting compound **362** for 3-hydroxypyridine and (R)-(+)-3-pyrrolidinol for (S)-(-)-3-pyrrolidinol. (14mg, 12% yield) ^{1}H NMR: (Acetone-d_6) δ(ppm): 8.85 (s, 1H), 8.31 (d, J=2.9 Hz, 1H), 8.19 (dd, J=4.5, 1.2 Hz, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.42 (ddd, J=8.4, 2.9, 1.4 Hz, 1H), 7.31 (ddd, J=8.4, 4.7, 0.8 Hz, 1H), 7.26 (d, J=7.8, 1.6Hz, 1H), 6.97 (td, J=7.2, 1.6 Hz, 1H), 6.85 (dd, J=7.8, 1.2 Hz, 1H), 6.68 (d, J=8.8Hz, 6.66 (td, J= 7.6, 1.4 Hz, 1H), 3.56-5.33 (m, 1H), 4.60 (bs, 2H), 3.86 (dd, J=11.3, 4.7 Hz, 1H), 3.62-3.57 (m, 3H), 2.50-2.35 (m, 2H). m/z: 375.2 (MH$^+$).

Example 197:

(S)-N-(2-Aminophenyl)-4-(3-(phenylamino)pyrrolidin-1-yl)benzamide (369)

[0854] The title compound was obtained following the same procedures described in scheme 69, example 193 but substituting compound 3-aminopyridine for aniline. (7 mg, 16% yield) ^1H NMR: (Acetone-d_6) δ(ppm): 8.84 (s, 1H), 7.91 (d, J=8.8 Hz, 2H), 7.25 (dd, J=7.8, 1.2 Hz, 1H), 7.12 (t, J=7.2 Hz, 2H), 6.96 (dt, J=8.0, 1.4 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.71 (dd, J=8.8, 1.0 Hz, 2H), 6.66 (t, J=7.8 Hz, 1H), 6.62 (d, J=8.8 Hz, 2H), 5.26 (d, J=7.6 Hz, 1H), 4.60 (bs, 1H), 4.30 (quint, J=5.3 Hz, 1H), 3.79 (dd, J=10.0 Hz, 1H), 3.57 (q, J=9.6 Hz, 1H), 3.50-3.45 (m, 1H), 3.30 (dd, J=10.2, 3.9 Hz, 1H), 2.42 (sext, J=6.8 Hz, 1H). m/z: 373.1 (MH^+).

Example 198:

(R)-N-(2-Aminophenyl)-4-(3-(phenylamino)pyrrolidin-1-yl)benzamide (370)

[0855] The title compound was obtained following the same procedures described in scheme 69, example 193 but substituting 3-aminopyridine for aniline and (R)-(+)-3-pyrrolidinol for (S)-3-pyrrolidinol. (22 mg, 23% yield) ^1H NMR ($CDCl_3$) δ 7.79 (m, 2H), 7.2-7.4 (m, 2H), 7.05 (s, 1H), 6.8 (m, 3H) 6.65 (m, 2H), 6.53(m, 2H), 4.24 (br.s., 1H), 3.9(m, 2H), 3.73 (m, 1H), 3.26 (m, 1H), 2.37 (m, 1H), 2.09 (m, 1H) m/z: 373.3 (MH^+).

Example 199:

(S)-N-(2-Aminophenyl)-4-(3-phenoxypyrrolidin-1-yl)benzamide (371)

[0856] The title compound was obtained following the same procedures described in scheme 69, example 193 but skipping steps 1 and 4 and substituting compound **362** for phenol. (50 mg, 33% yield) ^1H NMR ($CDCl_3$) δ 7.79 (μ, 3H), 7.3 (m, 3H), 7.03 (m, 1H), 6.96 (m, 1H), 6.90 (d, 2H, J=8.8 Hz), 6.80 (m, 2H), 6.54 (d, J=8.8 Hz, 2H), 5.08 (br.s., 1H), 3.71 (dd, J=4.7 Hz, J=11.0 Hz, 1H), 3.6 (m, 3H), 2.41 (m, 1H), 2.31 (m, 1H) m/z: 374.2 (MH^+).

Example 200:

(S)-Methyl-4-(1-(4-(2-aminophenylcarbamoyl)phenyl)pyrrolidin-3-yloxy)benzoate (372)

[0857] The title compound was obtained following the same procedures described in scheme 69, example 193 but skipping steps 1 and 4 and substituting compound **362** for methyl 4-hydroxybenzoate. (143 mg, 42% yield) ^1H NMR ($CDCl_3$) δ 8.0 (m, 2H), 7.81 (m, 2H), 7.72 (s, 1H), 7.25 (m, 1H), 7.06 (m, 1H), 6.91(m, 2H), 6.84 (m, 2H), 6.59 (m, 2H), 5.16 (br.s., 1H), 3.9(s, 3H), 3.78 (m, 1H), 3.60 (m, 3H), 2.4 (m, 2H) m/z: 432.4 (MH^+).

Example 201:

(S)-4-(1-(4-(2-Aminophenyl carbamoyl)phenyl)pyrrolidin-3-yloxy)benzoic acid (373)

[0858] A solution of **372** (100 mg, 0.23 mmol) and KOH (100 mg, 1.78 mmol) in 1:1:1 mixture of THF/water/MeOH (6 mL) was stirred at room temperature for 5 days. The reaction mixture was concentrated and partitioned between water (5 mL) and ether (5 mL). Organic phase

was discarded and the aqueous phase was acidified to pH=6 using 1M HCl solution and extracted with EtOAc. The extract was dried over Na_2SO4, filtered and concentrated. The residue was purified by flash chromatography, eluent MeOH-DCM (gradient of MeOH from 5 till 20% MeOH) to afford the title compound (20 mg, 21% yield). ^{1}H NMR (DMSO) δ 9.34 (σ, 1H), 7.85 (m, 4H), 7.11 (d, 1H, J=7.8 Hz), 7.00 (d, J=8.4 Hz, 2H), 6.92 (d, 2H, J=7.7 Hz), 6.75 (d, J=8.0 Hz, 2H), 6.6 (m, 3H), 5.26 (br.s., 1H), 3.75 (m, 1H), [3.34 DMSO, 4H], 2.44 (m, 1H), 2.31 (m, 1H) m/z: 418.4 (MH^+).

Example 202

(S)-N-(2-Aminophenyl)-4-(3-(3,4,5-trimethoxyphenoxy)pyrrolidin-1-yl)benzamide (374)

[0859] The title compound was obtained following the same procedures described in scheme 69, example 193 but skipping steps 1 and 4 and substituting compound **362** for 3,4,5-trimethoxyphenol. (30 mg, 21%) ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 2H, J=8.8Hz), 7.73 (s, 1H), 7.26 (d, 1H, J=7.4 Hz), 7.05 (t, J=7.7 Hz, 1H), 6.81 (d, 2H, J=7.7 Hz), 6.57 (d, J=8.7 Hz, 2H), 6.14 (s, 2H), 5.04 (br.s., 1H), 3.88 (s, 6H), 3.80 (s, 3H), 3.71 (dd, J=4.7 Hz, J=11.0 Hz, 1H), 3.6 (m, 3H), 2.41 (m, 1H), 2.31 (m, 1H) m/z: 464.4 (MH^+).

Example 203:

(S)-N-(2-Aminophenyl)-4-(3-(benzo[d][1,3]dioxol-5-yloxy)pyrrolidin-1-yl)benzamide (375)

[0860] The title compound was obtained following the same procedures described in scheme 69, example 193 but skipping steps 1 and 4 and substituting compound **362** for benzo[d][1,3]dioxol-5-ol. (31 mg, 15%) ^{1}H NMR ($CDCl_3$) δ8.95 (s, 1H), 7.87 (d, 2H, J=8.0Hz), 7.80 (d, J=8.7 Hz, 1H), 7.67 (s, 1H), 7.48 (s, .5H) 7.04 (m, 1H), 6.83(m, 1H), 6.71 (m, 1H), 6.57 (d, 2H), 6.48 (s, 1H), 6.33 (m, 1H), 5.93 (s, 2H), 4.96 (br.s., 1H), 3.67(m, 1H), 3.57 (m, 3H), 2.36 (m, 1H), 2.26 (m, 1H) m/z: 418.2 (MH^+).

Example 204:

(S)-N-(2-Aminophenyl)-4-(3-(4-phenoxyphenoxy)pyrrolidin-1-yl)benzamide (376)

[0861] The title compound was obtained following the same procedures described in scheme 69, example 193 but skipping steps 1 and 4 and substituting compound **362** for 4-phenoxyphenol. ^{1}H NMR ($CDCl_3$) δ 7.81 (m, 2H), 7.70 (s, 1H), 7.67 (s, .5H), 7.2-7.4 (m, 4 H) 6.8-7.2 (m, 10H), 6.6(m, 2H), 5.05 (br.s., 1H), 3.6(m, 1H), 3.5 (m, 3H), 2.41 (m, 1H), 2.32 (m, 1H) m/z: 466.4 (MH^+).

Example 205:

(S)-N-(2-Aminophenyl)-4-(3-(4-nitrophenoxy)pyrrolidin-1-yl)benzamide (377)

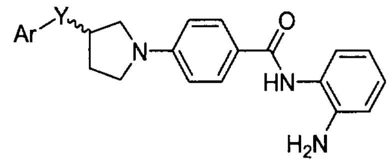
[0862] The title compound was obtained following the same procedures described in scheme 69, example 193 but skipping steps 1 and 4 and substituting compound **362** for 4-nitrophenol. (12 mg, 6%) ^{1}H NMR (CDCl$_3$) δ 8.12 (d, 2H, J=9.1 Hz), 7.72 (d, J=8.8 Hz, 2H), 7.18 (d, J=7.3 Hz, 1H), 6.97 (t, 1H, J=7.7 Hz), 6.87 (d, J=9.1 Hz, 2H), 6.50 (d, 2H, J=8.6Hz), 5.09 (br.s., 1H), 3.71 (dd, J=4.5 Hz, J=11.3 Hz, 1H), 3.6 (m, 3H2.3 (m, 2H) m/z: 419.1 (MH$^+$).

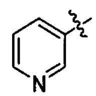
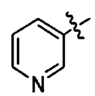
Example 206:

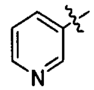
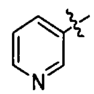
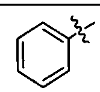
(S)-N-(2-Aminophenyl)-4-(3-(pyridin-2-ylthio)pyrrolidin-1-yl)benzamide (378)

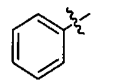
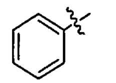
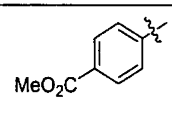
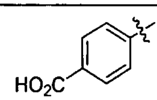
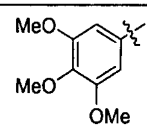
[0863] The title compound was obtained following the same procedures described in scheme 69, example 193 but skipping steps 1 and 4 and substituting compound **362** for pyridine-2-thiol. (22 mg, 28%) ^{1}H NMR (CDCl$_3$) δ 8.44 (μ, 1H), 7.78 (d, J=8.8 Hz, 2H), 7.69 (s, 1H), 7.49 (t, 1H, J=7.4 Hz), 7.27 (m, 1H), 7.18 (d, 1H, J=8.0Hz), 7.0-7.1 (m, 2H), 6.82 (d, 7.8 Hz, 2H), 6.55 (d, J=9.0 Hz, 2H), 4.55 (m, 1H), 3.9-4.0 (m, 3H), 3.4-3.6 (m, 4H) 2.6 (m, 1H), 2.2 (m, 1H) m/z: 391.0 (MH$^+$).

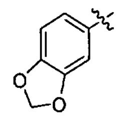
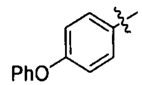
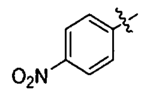
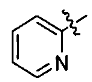
Table 13. Characterization of examples 193-206 prepared according to the scheme 69.



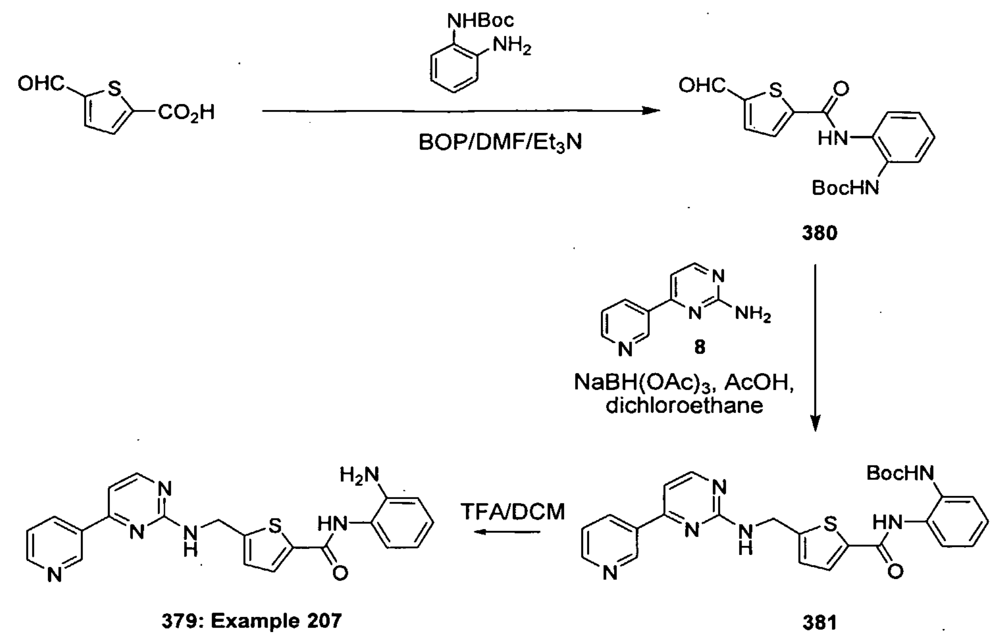
Ex.	Cpd	Ar	Y	Name	Characterization
193	361		NH	(S)-N-(2-aminophenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide	[1]H NMR: (CD_3OD) δ(ppm): 7.97 (d, J=2.7 Hz, 1H), 7.86 (d, J=8.8 Hz, 2H), 7.78 (dd, J=4.7, 1.0 Hz, 1H), 7.18-7.10 (m, 3H), 7.05 (td, J=7.4, 0.6 Hz, 1H), 6.89 (dd, J=7.8, 1.2 Hz, 1H), 6.76 (td, J=7.4, 1.4 Hz, 1H), 6.64 (d, J=8.8 Hz, 2H), 4.25 (quint, J=4.9 Hz, 1H), 3.77 (dd, J=10.2, 6.1 Hz, 1H), 3.57 (dd, J=17.0, 7.0 Hz, 1H), 3.49 (td, J=8.0, 5.3 Hz, 1H), 3.29 (q, J=6.7Hz, 1H), 2.41 (sext, J=7.2 Hz, 1H), 2.10 (sext, J=4.9 Hz, 1H).
194	366		NH	(R)-N-(2-aminophenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide	[1]H NMR: (DMSO-d_6) δ(ppm): 9.34 (s, 1H), 8.00 (d, J=2.3 Hz, 1H), 7.84 (d, J=8.8 Hz, 2H), 7.77 (dd, J=4.7, 1.2 Hz, 1H), 7.12 (d, J=7.6 Hz, 1H), 7.08 (dd, J=8.0, 4.5 Hz, 1H), 6.99-6.97 (m, 1H), 6.92 (t, J=7.8 Hz, 1H), 6.75 (d, J=7.8 Hz, 1H), 6.60-6.56 (m, 3H), 6.17 (d, J=6.8 Hz, 1H), 4.81 (s, 2H), 4.19-4.17 (m, 1H), 3.71 (dd, J=10.2, 6.5 Hz, 1H), 3.53-3.47 (m, 1H), 3.42-3.38 (m, 1H), 3.18 (dd, J=10.4, 4.1 Hz, 1H), 2.32 (sext, J=6.3 Hz, 1H), 1.99 (sext, J=4.7 Hz, 1H).

Ex.	Cpd	Ar	Y	Name	Characterization
195	367		O	(S)-N-(2-aminophenyl)-4-(3-(pyridin-3-yloxy)pyrrolidin-1-yl)benzamide	^{1}H NMR: (Acetone-d_6) δ(ppm): 8.88 (s, 1H), 8.31 (d, J=2.9 Hz, 1H), 8.19 (d, J=4.7 Hz, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.41 (ddd, J=8.4, 2.9, 1.4 Hz, 1H), 7.31 (ddd, J=8.4, 4.5, 0.6 Hz, 1H), 7.26 (d, J=7.8 Hz, 1H), 6.97 (td, J=7.8, 1.4 Hz, 1H), 6.85 (dd, J=8.0, 1.4 Hz, 1H), 6.66 (d, J=9.0 Hz, 2H), 6.65 (td, J=8.0, 1.4 Hz, 1H), 5.34-5.32 (m, 1H), 4.62 (s, 2H), 3.84 (dd, J=11.3, 4.7 Hz, 1H), 3.61-3.56 (m, 3H), 2.50-2.34 (m, 2H).
196	368		O	(R)-N-(2-aminophenyl)-4-(3-(pyridin-3-yloxy)pyrrolidin-1-yl)benzamide	^{1}H NMR: (Acetone-d_6) δ(ppm): 8.85 (s, 1H), 8.31 (d, J=2.9 Hz, 1H), 8.19 (dd, J=4.5, 1.2 Hz, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.42 (ddd, J=8.4, 2.9, 1.4 Hz, 1H), 7.31 (ddd, J=8.4, 4.7, 0.8 Hz, 1H), 7.26 (d, J=7.8, 1.6Hz, 1H), 6.97 (td, J=7.2, 1.6 Hz, 1H), 6.85 (dd, J=7.8, 1.2 Hz, 1H), 6.68 (d, J=8.8Hz, 6.66 (td, J= 7.6, 1.4 Hz, 1H), 3.56-5.33 (m, 1H), 4.60 (bs, 2H), 3.86 (dd, J=11.3, 4.7 Hz, 1H), 3.62-3.57 (m, 3H), 2.50-2.35 (m, 2H).
197	369		NH	(S)-N-(2-aminophenyl)-4-(3-(phenylamino)pyrrolidin-1-yl)benzamide	^{1}H NMR: (Acetone-d_6) δ(ppm): 8.84 (s, 1H), 7.91 (d, J=8.8 Hz, 2H), 7.25 (dd, J=7.8, 1.2 Hz, 1H), 7.12 (t, J=7.2 Hz, 2H), 6.96 (dt, J=8.0, 1.4 Hz, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.71 (dd, J=8.8, 1.0 Hz, 2H), 6.66 (t, J=7.8 Hz, 1H), 6.62 (d, J=8.8 Hz, 2H), 5.26 (d, J=7.6 Hz, 1H), 4.60 (bs, 1H), 4.30 (quint, J=5.3 Hz, 1H), 3.79 (dd, J=10.0 Hz, 1H), 3.57 (q, J=9.6 Hz, 1H), 3.50-3.45 (m, 1H), 3.30 (dd, J=10.2, 3.9 Hz, 1H), 2.42 (sext, J=6.8 Hz, 1H).

Ex.	Cpd	Ar	Y	Name	Characterization
198	**370**		NH	(R)-N-(2-aminophenyl)-4-(3-(phenylamino)pyrrolidin-1-yl)benzamide	^{1}H NMR ($CDCl_3$) δ (ppm) 7.79 (m, 2H), 7.2-7.4 (m, 2H), 7.05 (s, 1H), 6.8 (m, 3H) 6.65 (m, 2H), 6.53(m, 2H), 4.24 (br.s., 1H), 3.9(m, 2H), 3.73 (m, 1H), 3.26 (m, 1H), 2.37 (m, 1H), 2.09 (m, 1H)
199	**371**		O	(S)-N-(2-aminophenyl)-4-(3-phenoxypyrrolidin-1-yl)benzamide	^{1}H NMR ($CDCl_3$) δ (ppm) 7.79 ((m, 3H), 7.3 (m, 3H), 7.03 (m, 1H), 6.96 (m, 1H), 6.90 (d, 2H, J=8.8 Hz), 6.80 (m, 2H), 6.54 (d, J=8.8 Hz, 2H), 5.08 (br.s., 1H), 3.71 (dd, J=4.7 Hz, J=11.0 Hz, 1H), 3.6 (m, 3H), 2.41 (m, 1H), 2.31 (m, 1H)
200	**372**		O	(S)-methyl-4-(1-(4-(2-aminophenyl carbamoyl)phenyl)pyrrolidin-3-yloxy)benzoate	^{1}H NMR ($CDCl_3$) δ (ppm): 8.0 (m, 2H), 7.81 (m, 2H), 7.72 (s, 1H), 7.25 (m, 1H), 7.06 (m, 1H), 6.91(m, 2H), 6.84 (m, 2H), 6.59 (m, 2H), 5.16 (br.s., 1H), 3.9(s, 3H), 3.78 (m, 1H), 3.60 (m, 3H), 2.4 (m, 2H)
201	**373**		O	(S)-4-(1-(4-(2-aminophenyl carbamoyl)phenyl)pyrrolidin-3-yloxy)benzoic acid	^{1}H NMR: (DMSO-d_6) δ(ppm): 9.34 (s, 1H), 7.85 (m, 4H), 7.11 (d, 1H, J=7.8 Hz), 7.00 (d, J=8.4 Hz, 2H), 6.92 (d, 2H, J=7.7 Hz), 6.75 (d, J=8.0 Hz, 2H), 6.6 (m, 3H), 5.26 (br.s., 1H), 3.75 (m, 1H), [3.34 DMSO, 4H], 2.44 (m, 1H), 2.31 (m, 1H)
202	**374**		O	(S)-N-(2-aminophenyl)-4-(3-(3,4,5-trimethoxyphenoxy)pyrrolidin-1-yl)benzamide	^{1}H NMR ($CDCl_3$) δ (ppm) 7.79 (d,2H; , J=8.8Hz), 7.73 (s, 1H), 7.26 (d, 1H, J=7.4 Hz), 7.05 (t, J=7.7 Hz, 1H), 6.81 (d, 2H, J=7.7 Hz), 6.57 (d, J=8.7 Hz, 2H), 6.14 (s, 2H), 5.04 (br.s., 1H), 3.88 (s, 6H), 3.80 (s, 3H), 3.71 (dd, J=4.7 Hz, J=11.0 Hz, 1H), 3.6 (m, 3H), 2.41 (m, 1H), 2.31 (m, 1H)

Ex.	Cpd	Ar	Y	Name	Characterization
203	375		O	(S)-N-(2-aminophenyl)-4-(3-(benzo[d][1,3]dioxol-5-yloxy)pyrrolidin-1-yl)benzamide	^{1}H NMR ($CDCl_3$) δ (ppm) 8.95 (s, 1H), 7.87 (d, 2H, J=8.0Hz), 7.80 (d, J=8.7 Hz, 1H), 7.67 (s, 1H), 7.48 (s, .5H) 7.04 (m, 1H), 6.83(m, 1H), 6.71 (m, 1H), 6.57 (d, 2H), 6.48 (s, 1H), 6.33 (m, 1H), 5.93 (s, 2H), 4.96 (br.s., 1H), 3.67(m, 1H), 3.57 (m, 3H), 2.36 (m, 1H), 2.26 (m, 1H)
204	376		O	(S)-N-(2-aminophenyl)-4-(3-(4-phenoxyphenoxy)pyrrolidin-1-yl)benzamide	^{1}H NMR ($CDCl_3$) δ (ppm) 7.81 (m, 2H), 7.70 (s, 1H), 7.67 (s, .5H), 7.2-7.4 (m, 4 H) 6.8-7.2 (m, 10H), 6.6(m, 2H), 5.05 (br.s., 1H), 3.6(m, 1H), 3.5 (m, 3H), 2.41 (m, 1H), 2.32 (m, 1H)
205	377		O	(S)-N-(2-aminophenyl)-4-(3-(4-nitrophenoxy)pyrrolidin-1-yl)benzamide	^{1}H NMR ($CDCl_3$) δ (ppm) 8.12 (d, 2H, J=9.1 Hz), 7.72 (d, J=8.8 Hz, 2H), 7.18 (d, J=7.3 Hz, 1H), 6.97 (t, 1H, J=7.7 Hz), 6.87 (d, J=9.1 Hz, 2H), 6.50 (d, 2H, J=8.6Hz), 5.09 (br.s., 1H), 3.71 (dd, J=4.5 Hz, J=11.3 Hz, 1H), 3.6 (m, 3H2.3 (m, 2H)
206	378		S	(S)-N-(2-aminophenyl)-4-(3-(pyridin-2-ylthio)pyrrolidin-1-yl)benzamide	^{1}H NMR ($CDCl_3$) δ (ppm) 8.44 (m, 1H), 7.78 (d, J=8.8 Hz, 2H), 7.69 (s, 1H), 7.49 (t, 1H, J=7.4 Hz), 7.27 (m, 1H), 7.18 (d, 1H, J=8.0Hz), 7.0-7.1 (m, 2H), 6.82 (d, 7.8 Hz, 2H), 6.55 (d, J=9.0 Hz, 2H), 4.55 (m, 1H), 3.9-4.0 (m, 3H), 3.4-3.6 (m, 4H) 2.6 (m, 1H), 2.2 (m, 1H)

Scheme 70



Example 207:

N-(2-Aminophenyl)-5-((4-(pyridin-2-yl)pyrimidin-2-ylamino)methyl)thiophene-2-carboxamide (379)

[0864] Step 1. tert-Butyl 2-(5-formylthiophene-2-carboxamido)phenylcarbamate (380)

[0865] A solution of 5-formylthiophene-2-carboxylic acid (350 mg, 2.24 mmol), tert-butyl 2-aminophenylcarbamate (467 mg, 2.24 mmol) and triethylamine (470 μL, 340 mg, 3.36 mmol) and BOP (1.1 g, 2.68 mmol) in DMF (10 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated and purified by flash chromatography using 25% EtOAc in hexanes as an eluent, yielding 260 mg (33%) of the title compound. ^{1}H NMR (CDCl3) δ9.95 (s, 1H), 9.7 (br. s, 1H), 7.84 (d, 1H, J=8.0 Hz), 7.74 (m, 2H), 7.15 (m, 2H), 6.72 (s, 1H), 1.56 (s, 9H). LRMS: (calc) 346.1; (found) 369.1 (M+Na)

[0866] Step 2. tert-Butyl 2-(5-((4-(pyridin-2-yl)pyrimidin-2-ylamino)methyl)thiophene-2-carboxamido)phenylcarbamate (381)

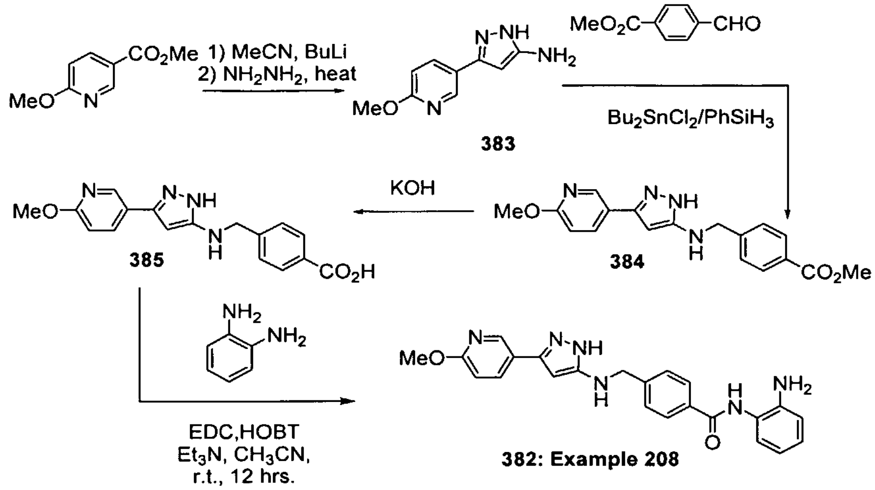
[0867] A solution of aldehyde **380** (260 mg, 0.75 mmol), 4-(pyridin-3-yl)pyrimidin-2-amine (85 mg, 0.5 mmol) and acetic acid (100 μL) in DCE (2 mL) was treated with $NaBH(OAc)_3$ (22 mg, 1 mmol) and the resultant mixture was stirred at room temperature overnight. It was then quenched by addition of saturated $NaHCO_3$ (5 mL) and the aqueous phase was extracted with EtOAc. Organic extract was dried with Na_2SO_4, filtered and concentrated to provide a crude product

which was purified by flash chromatography using 80-20% mixture EtOAc-hexane as an eluent, to afford the title compound (35 mg, 14% yield). LRMS: (calc) 502.2; (found) 503.4 ($M+H^1$)

N-(2-Aminophenyl)-5-((4-(pyridin-2-yl)pyrimidin-2-ylamino)methyl)thiophene-2-carboxamide (379)

[0868] A solution of **381** (35 mg, 0.07 mmol) in 1:1 mixture of DCM and TFA (4 mL) was stirred at room temperature for 30 minutes. The reaction mixture was concentrated to produce a solid which was triturated with ether to afford the title compound as a TFA salt (26 mg, 75% yield). ^{1}H NMR (MeOH-d4) δ9.31 (s, 1H), 8.68 (s, 1H), 8.66 (s, 1H), 8.43 (d, J=5.1Hz, 1H), 7.77 (d, J=3.9 Hz, 1H), 7.68 (m, 1H), 7.1-7.5 (m, 6H). LRMS: (calc) 402.2; (found) 403.3 ($M+H^1$).

<u>Scheme 71</u>



Example 208:

N-(2-Aminophenyl)-4-((3-(6-methoxypyridin-3-yl)-1H-pyrazol-5-ylamino)methyl) benzamide (382)

[0869] <u>Step 1: 3-(6-Methoxypyridin-3-yl)-1H-pyrazol-5-amine (383)</u>

[0870] MeCN (940 μL, 736 mg, 17.96 mmol) in THF (20 mL) was treated with 2.5 M solution of BuLi in hexanes (7.2 mL, 17.96 mmol) at -78°C and the reaction mixture was allowed to stir at the same temperature for 30 min, treated with a solution of methyl 6-methoxynicotinate (2 g, 11.96 mmol) in THF (10 mL) at -78°C and was stirred at room temperature for additional 2 hours. It was then quenched by addition of water (10 mL) and 1M solution of HCl (10 mL). The resultant mixture was concentrated in *vacuo*, the residue was mixed with hydrazine monohydrate (5 mL) in EtOH (30 mL), refluxed for 2 hours, cooled and concentrated under reduced pressure produce a solid which was purified by flash chromatography using 10% MeOH in DCM as an eluent, to afford the title compound (720 mg, 32% yield). ^{1}H NMR (MeOH-d4) δ8.39 (s, 1H), 7.89 (d, J=8.6 Hz,

1H), 6.80 (d, J=8.6 Hz, 1H), 5.85 (s, 1H), 3.91 (s, 3H). LRMS: (calc) 190.1; (found) 191.1 ($M+H^1$).

[0871] Step 2: Methyl 4-((3-(6-methoxypyridin-3-yl)-1H-pyrazol-5-ylamino)methyl)benzoate (384)

[0872] A solution of amine **383** (720 mg, 3.79 mmol), methyl 4-formylbenzoate (745 mg, 4.54 mmol), and Bu_2SnCl_2 (230 mg, 0.76 mmol) in dry THF (5 mL) was stirred at room temperature for 2 hours. It was then treated with $PhSiH_3$ (514 µL, 451 mg, 4.17 mmol) and allowed to stir for another hour at room temperature. The reaction mixture was quenched by addition of MeOH and vigorous stirring for 45 min. It was then concentrated in *vacuo* and the residue was purified by flash chromatography using the gradient 50-100% EtOAc in hexane to afford the title compound (672 mg, 52% yield). LRMS: (calc) 338.1; (found) 339.2 ($M+H^1$)

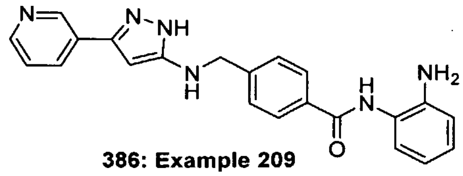
[0873] Step 3: 4-((3-(6-Methoxypyridin-3-yl)-1H-pyrazol-5-ylamino)methyl)benzoic acid (385)

[0874] A solution of **384** (672mg, 1.99 mmol) and KOH (300 mg, 5.35 mmol) in 1:1:1 mixture of THF, MeOH and water (9 mL) was stirred at room temperature overnight. The reaction mixture was acidified to pH=4 by addition of 1M HCl and concentrated in *vacuo*. The residue was triturated with water and the solid was collected by filtration and dried to afford the title compound (640mg, 99% yield). LRMS: (calc) 324.1; (found) 325.2 ($M+H^1$)

[0875] Step 4: N-(2-Aminophenyl)-4-((3-(6-methoxypyridin-3-yl)-1H-pyrazol-5-ylamino) methyl)benzamide (382)

[0876] A solution of **385** (640 mg, 1.97 mmol) in MeCN (10 mL) was sequentially treated with Et_3N (831 µL, 603 mg, 5.96 mmol), EDC (571 mg, 2.98 mmol), HOBT (334 mg, 2.18 mmol) and 1,2-phenylene diamine (429 mg, 3.97 mmol) and allowed to stir overnight. The reaction mixture was concentrated and partitioned between DCM (15 mL) and saturated NH_4Cl (15 mL). The organic phase was collected, dried with Na_2SO_4, filtered and concentrated. The resultant solid was purified by flash chromatography using the gradient 3-15% MeOH in DCM to afford the title compound (113 mg, 14% yield).^{1}H NMR (DMSO-d6) δ9.65 (s, 1H), 8.43 (s, 1H), 7.92 (m, 3H), 7.48 (d, J=8.0 Hz, 2H), 7.16 (d, J=7.4 Hz, 1H), 6.97 (t, J=7.6 Hz, 1H), 6.81 (t, J=8.2 Hz, 2H), 6.63 (t, J=7.4 Hz, 1H), 5.85 (s, 1H), 4.34 (s, 2H), 3.85 (s, 3H). LRMS: (calc) 414.2; (found) 415.3 ($M+H^1$)

Example 209: **N-(2-aminophenyl)-4-((3-(pyridin-3-yl)-1H-pyrazol-5-ylamino)methyl)benzamide (386)**

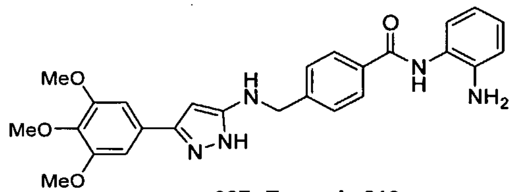


386: Example 209

[0877] Title compound was prepared according to the scheme 71 (example 208) starting from methyl nicotinate. ^{1}H NMR (MeOH-d4) δ8.80 (s, 1H), 8.43 (d, J=3.9 Hz, 1H), 8.04 (m, 2H), 7.94 (d, J=8.2 Hz, 2H), 7.53 (d, J=8.2 Hz, 1H), 7.43 (m, 1H), 7.15 (d, J=7.6 Hz, 1H), 7.05 (t, J=7.2 Hz, 2H), 6.88 (d, J=8.0 Hz, 1H), 6.75 (t, J=7.4 Hz, 1H), 5.94 (s, 1H), 4.45 (s, 2H). LRMS: (calc) 384.2; (found) 385.2 (M+H^1)

Example 210:

N-(2-Aminophenyl)-4-((3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-5-ylamino)methyl) benzamide (387)

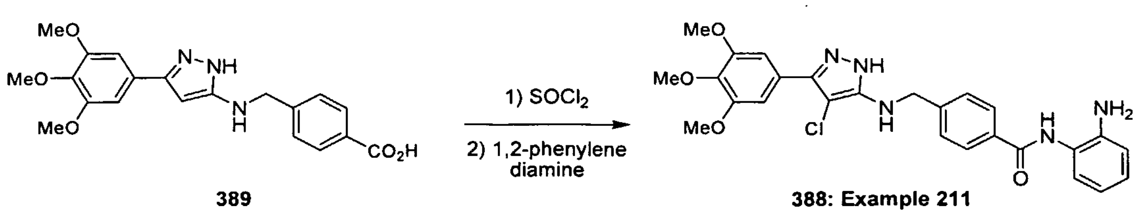


387: Example 210

[0878] Title compound was prepared according to the scheme 71 (example 208) starting from methyl 3,4,5-trimethoxybenzoate. ^{1}H NMR (MeOH-d4) δ7.92 (d, J=8.4 Hz, 2H), 7.53 (d, J=8.0 Hz, 2H), 7.16 (d, J=7.9 Hz, 1H), 7.06 (t, J=7.8 Hz, 1H), 6.93 (s, 2H), 6.88 (d, J=8.0 Hz, 1H), 6.75 (t, J=7.6 Hz, 1H), 5.89 (s, 1H), 4.45 (s, 2H), 3.87 (s, 6H), 3.77 (s, 3H). LRMS: (calc) 473.3; (found) 474.4 (M+H^1)

Example 211:

N-(2-Aminophenyl)-4-((4-chloro-3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-5-ylamino) methyl)benzamide (388)



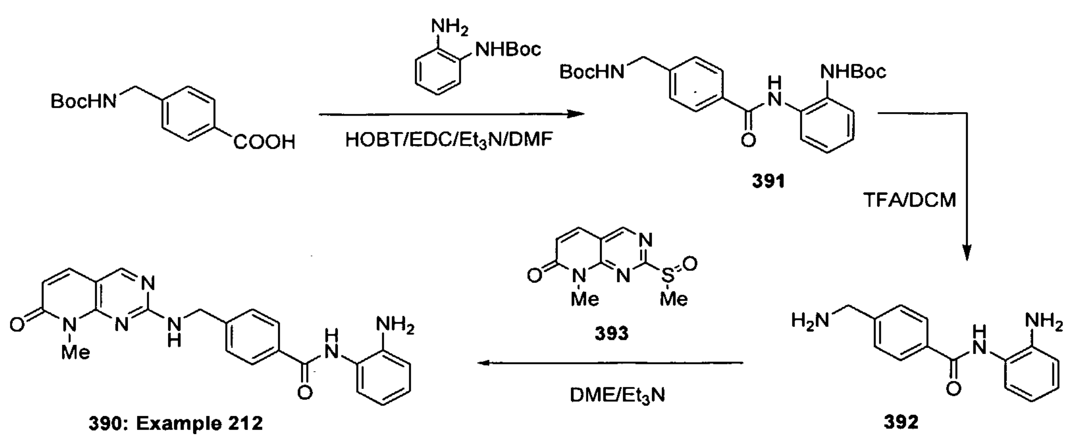
[0879] Steps 1, 2 and 3. 4-((3-(3,4,5-Trimethoxyphenyl)-1H-pyrazol-5-ylamino)methyl)benzoic acid (389)

[0880] Title compound was obtained according to the scheme 71, steps 1, 2 and 3 using in the first step methyl 3,4,5-trimethoxybenzoate instead of methyl 6-methoxynicotinate.LRMS: (calc) 383.1; (found) 384.2 (M+H[1]).

[0881] Step 4: N-(2-Aminophenyl)-4-((4-chloro-3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-5-ylamino)methyl)benzamide (388)

[0882] A solution of **389** (30 mg, 0.08 mmol) in a 1:1 mixture of DCM and SOCl2 (2 mL) was stirred at room temperature for 30 min. The reaction mixture was concentrated and treated with a solution of 1,2-phenylene diamine (18 mg, 0.16 mmol) in THF (2 mL) and stirred at room temperature for 15 min, concentrated under reduced pressure to produce a solid which was purified by preparative HPLC (column AQUASIL C-18; 5 μM; 230 x 21.2 mm; eluent 30-95% MeOH in water) to afford the title compound (8 mg, 20% yield). ^{1}H NMR (MeOH-d4) δ7.92 (d, J=8.3 Hz, 2H), 7.52 (d, J=8.2 Hz, 2H), 7.17 (d, J=7.6 Hz, 1H), 7.06 (m, 3H), 6.89 (d, J=7.8 Hz, 1H), 6.75 (t, J=7.2 Hz, 1H), 4.55 (s, 2H), 3.89 (s, 6H), 3.80 (s, 3H). LRMS: (calc) 507.2; (found) 508.3 (M+H[1]).

Scheme 72



Example 212:

N-(2-Aminophenyl)-4-((8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)methyl)benzamide (389)

[0883] Step 1. tert-Butyl 2-(4-(Boc-aminomethyl)benzamido)phenylcarbamate (391)

[0884] A solution of 4-((tert-butoxycarbonylamino)methyl)benzoic acid(1 g, 3.98 mmol) in DMF (10 mL) was treated sequentially with EDC (930 mg, 4.84 mmol), HOBT (682 mg, 4.46 mmol) and Et_3N (670 μL, 489 mg, 4.84 mmol) at room temperature and allowed to stir overnight. The

reaction mixture was concentrated under reduced pressure and partitioned between chloroform (10 mL) and water (10 mL). Organic phase was collected, washed with 1M HCl (10 mL) and saturated $NaHCO_3$ (10 mL), dried, filtered and evaporated to form a residue which was purified by flash chromatography using 30% EtOAc in hexanes as an eluent to afford the title compound (840 mg, 51%). LRMS: (calc) 441.2; (found) 442.2 ($M+H^1$)

[0885] Step 2. 4-(Aminomethyl)-N-(2-aminophenyl)benzamide (392)

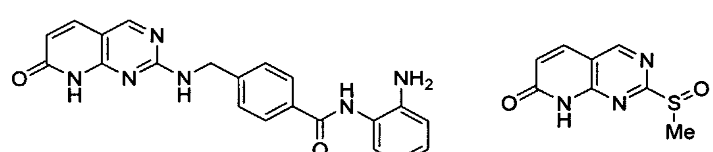
[0886] A solution of **391** (840 mg, 1.9 mmol) in 2:1 mixture of DCM/TFA (6 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford the title compound as a mixture of the mono and di-TFA salt. (1.33 g, 100 % yield). . LRMS: (calc) 241.2; (found) 242.2 ($M+H^1$).

[0887] Step 3. N-(2-Aminophenyl)-4-((8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)methyl)benzamide (390)

[0888] A solution of sulfoxide **393** (Barvian, M. *et al. J. Med. Chem.* (**2001**) *44*(6); 1016-1016) (166 mg, 0.74 mmol), bis-amine **392** (535 mg, 2.23 mmol) and triethylamine (620 μL, 4.46 mmol) in DME (3 mL) was stirred at room temperature for 3 hours. The reaction mixture was concentrated and partitioned between EtOAc (5 mL) and water (5 mL). Organic phase was collected and washed successively with saturated solutions of NH_4Cl (5 mL) and $NaHCO_3$ (5 mL), dried over Mg_2SO_4, filtered and concentrated to produce a residue which was triturated with 1:1 EtOAc/ hexane solution to afford the title compound (48 mg, 16% yield). ^1H NMR ($CDCl_3$) δ3.62 (s, 3H), 4.80 (m, 2H), 6.42 (d, J=10Hz, 1H), 6.85 (d, J=8Hz, 2H), 7.10 (m, 1H), 7.30 (m, 1H), 7.50 (m, 2H), 7.87 (s, 1H), 7.897 (m, 2H), 8.43 (s, 1H). LRMS: (calc) 400.0; (found) 401.0 ($M+H^1$)

Example 213:

N-(2-Aminophenyl)-4-((7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-ylamino)methyl) benzamide (394)

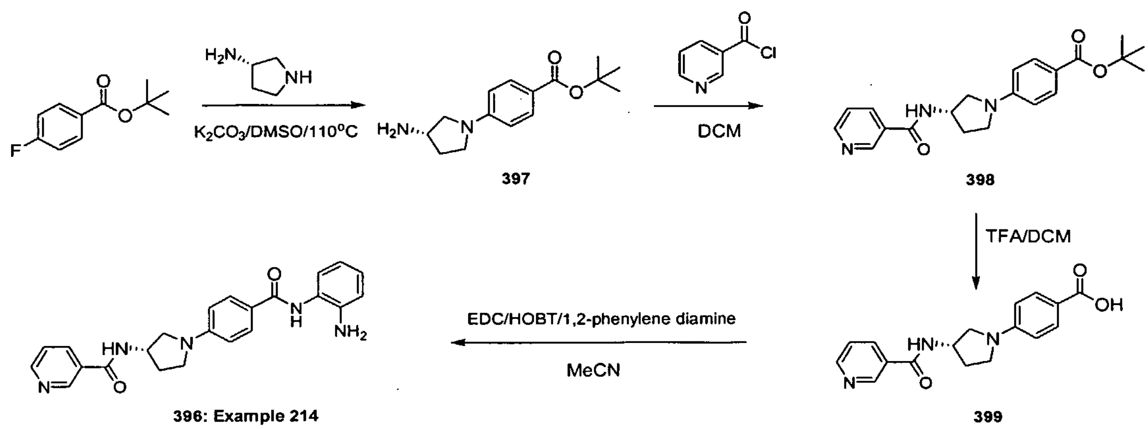


394: Example 213 **395**

[0889] Title compound was prepared in a similar manner as the example 212 (scheme 72) starting from the sulfoxide **395** obtained by literature procedure similarly to the sulfoxide **393.** ^1H NMR (DMSO) δ4.60 (s, 2H), 4.90 (s, 2H), 6.10 (d, J=10Hz, 1H), 6.55 (t, J=7Hz, 2H), 6.75 (m,

1H), 6.90 (t, J=7Hz, 2H), 7.10 (m, 2H), 7.40 (m, 2H), 7.65 (m, 1H), 7.90 (m, 1H), 8.55 (s, 1H), 9.69 (s, 1H). LRMS: (calc) 386.0; (found) 387.0 ($M+H^1$).

Scheme 73



Example 214:

(S)-N-(1-(4-(2-Aminophenyl carbamoyl)phenyl)pyrrolidin-3-yl)nicotinamide (396)

[0890] Step 1. (S)-*tert*-Butyl 4-(3-aminopyrrolidin-1-yl)benzoate (**397**)

[0891] Title compound was obtained similarly to the aminoester **363** using the same procedure as described in step 2, scheme 69. ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J=8.8 Hz, 1H), 6.46 (d, J=8.8 Hz, 1H), 3.75 (m, 1H), 3.35-3.6 (m, 3H), 3.06 (dd, J=4.7 Hz, J=9.8 Hz, 1H), 2.26 (m, 1H), 1.85 (m, 1H), 1.57 (s, 9H), LRMS: (calc) 262.1; (found) 263.0 ($M+H^1$).

[0892] Step 2. (S)-*tert*-Butyl 4-(3-(nicotinamido)pyrrolidin-1-yl)benzoate (**398**)

[0893] A solution of **397** (100 mg, 0.38 mmol), Et_3N (160 μL, 1.14 mmol) and nicotinoyl chloride HCl salt (68 mg, 0.38 mmol) in DCM (2 mL) was stirred at room temperature for 1 hour and quenched by adding saturated NH_4Cl sat solution (5 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated to produce a residue which was purified by flash chromatography using 5% MeOH in DCM as an eluent to afford the title compound (110 mg, 79% yield). LRMS: (calc) 367.2; (found). 368.1 ($M+H^1$).

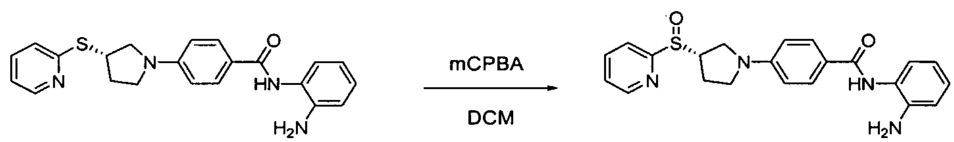
[0894] Step 3. (S)-4-(3-(Nicotinamido)pyrrolidin-1-yl)benzoic acid (**399**)

[0895] The title compound was obtained as the mixture of monosalt and disalt similarly to the compound **117** using the same procedure as described in step 5, scheme 28. LRMS: (calc) 311.1; (found) 312.1 ($M+H^1$).

[0896] Step 4. (S)-N-(1-(4-(2-Aminophenylcarbamoyl)phenyl)pyrrolidin-3-yl)nicotinamide (**396**)

[0897] A solution of **399** (93 mg, 0.3 mmol), phenylene diamine (65 mg, 0.6 mmol), EDC (86 mg, 0.45 mmol), HOBT (53 mg, 0.33 mmol) and Et_3N (125 μL, 91 mg, 0.9 mmol) in acetonitrile (2 mL) was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was purified by flash chromatography using the gradient 5-20% MeOH in DCM as an eluent to afford the title compound (24 mg, 16% yield). ^1H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.66 (d, J=4.9 Hz, 1H), 8.21 (d, J=3.9 Hz, 1H), 7.87 (d, 2H, J=8.8 Hz), 7.52 (dd, J=5.1 Hz, J=8.0 Hz, 1H), 7.15 (d, 1H, J=7.9 Hz), 7.05 (t, J=8.1 Hz, 1H), 6.89 (d, J=7.6 Hz, 1H), 6.76 (t, J=7.3 Hz, 1H), 6.66 (d, J= 9.0 Hz, 2H), 4.78 (m, 1H), 3.80 (dd, J=6.7 Hz, J=10.2 Hz, 1H), 3.61 (m, 1H), 3.49 (m, 1H), 3.41 (m, 1H), 2.4 (m, 1H), 2.2 (m, 1H). LRMS: (calc) 401.2; (found) 402.2 ($M+H^1$).

Scheme 74



378: Example 206 **400: Example 215**

Example 215:

<u>N-(2-Aminophenyl)-4-((S)-3-((S)-pyridin-2-ylsulfinyl)pyrrolidin-1-yl)benzamide (400)</u>

[0898] A solution of **378** (15 mg, 0.04 mmol) and mCPBA (6 mg, 0.04 mmol) in DCM (2 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated and the residue was purified by flash chromatography using the gradient EtOAc to 5% MeOH in DCM as an eluent, to afford the title compound (13 mg, 80% yield). ^1H NMR ($CDCl_3$) δ ^1H NMR ($CDCl_3$) δ 8.63 (m, 1H), 8.58 (m, 1H), 7.6-8.0 (m, 10H), 7.40 (m, 2H), 7.25 (m, 1H), 7.05 (m, 2H), 6.85 (m, 3H), 6.58 (d, J=8.8 Hz, 2H), 6.50 (d, J=11.1 Hz, 2H), 3.7-4.0 (m, 6H), 3.2-3.5 (m, 4H), 2.4-2.8 (m, 3H), 2.95 (m, 1H). LRMS: (calc) 406.1; (found) 407.1 ($M+H^1$).

Assay Example 1

Inhibition of Histone Deacetylase Enzymatic Activity

1. Human HDAC-1

[0899] Assay 1. HDAC inhibitors were screened against a cloned recombinant human HDAC-1 enzyme expressed and purified from a Baculovirus insect cell expression system. For deacetylase assays, 20,000 cpm of the [^{3}H]-metabolically labeled acetylated histone substrate (M. Yoshida *et al., J. Biol. Chem.* **265(28):** 17174-17179 (1990)) was incubated with 30 μg of the cloned recombinant hHDAC-1 for 10 minutes at 37 °C. The reaction was stopped by adding acetic acid (0.04 M, final concentration) and HCl (250 mM, final concentration). The mixture was extracted with ethyl acetate and the released [^{3}H]-acetic acid was quantified by scintillation counting. For inhibition studies, the enzyme was preincubated with compounds at 4 °C for 30 minutes prior to initiation of the enzymatic assay. IC_{50} values for HDAC enzyme inhibitors were determined by performing dose response curves with individual compounds and determining the concentration of inhibitor producing fifty percent of the maximal inhibition.

[0900] Assay 2. The following protocol was also used to assay the compounds of the invention. In the assay, the buffer used was 25mM HEPES, pH 8.0, 137mM NaCl, 2.7mM KCl, 1mM $MgCl_2$ and the subtrate was Boc-Lys(Ac)-AMC in a 50mM stock solution in DMSO. The enzyme stock solution was 4.08 μg/mL in buffer. The compounds were pre-incubated (2μl in DMSO diluted to 13 μl in buffer for transfer to assay plate) with enzyme (20μl of 4.08μg/ml) for 10 minutes at room temperature (35μl pre-incubation volume). The mixture was pre-incubated for 5 minutes at room temperature. The reaction was started by bringing the temperature to 37°C and adding 16 μl substrate. Total reaction volume was 50μl. The reaction was stopped after 20 minutes by addition of 50μl developer, prepared as directed by Biomol (Fluor-de-Lys developer, Cat. # KI-105). A plate was incubated in the dark for 10 minutes at room temperature before reading (λ_{Ex}=360nm, λ_{Em}=470nm, Cutoff filter at 435nm).

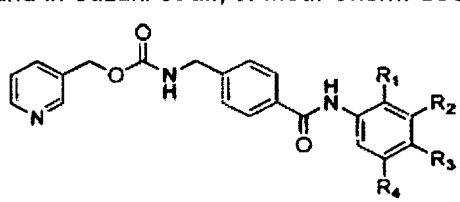
[0901] IC_{50} values for representative compounds are presented in Table 14. Assay 1 was used to measure HDAC activity of compounds 10c, 13e, 16d, 26b, 44, 47, 61a, 61b, 63, 134, 138, and 308. Assay 2 was used to measure HDAC activity of compounds 361, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, and 378. In Table 14, "a" indicates activity of ≤ 0.1 μM, "b" indicates activity of ≤ 1 μM, "c" indicates activity of ≤ 5 μM, and "d" indicates activity of > 5 μm. For the H4-Ac T24 EC vs. MS-275 assay in Table 14, "u" indicates less than 1, "v" indicates 1, and "w" indicates greater than 1. For the H3 Ac t24 assay in Table 14, "x" indicates activity of ≤ 1 μM, "y" indicates activity of ≤ 10 μM, and "z" indicates activity of ≤ 20 μM.

2. MTT Assay

[0902] HCT116 cells (2000/well) were plated into 96-well tissue culture plates one day before compound treatment. Compounds at various concentrations were added to the cells. The cells were incubated for 72 hours at 37°C in 5% CO_2 incubator. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide, Sigma) was added at a final concentration of 0.5 mg/ml and incubated with the cells for 4 hours before one volume of solubilization buffer (50% N,N-dimethylformamide, 20% SDS, pH 4.7) was added onto the cultured cells. After overnight incubation, solubilized dye was quantified by colorimetric reading at 570 nM using a reference at 630 nM using an MR700 plate reader (Dynatech Laboratories Inc.). OD values were converted to cell numbers according to a standard growth curve of the relevant cell line. The concentration which reduces cell numbers to 50% of that of solvent treated cells is determined as MTT IC_{50}. IC_{50} values for representative compounds are presented in Table 14. In Table 14, "a" indicates activity of ≤ 0.1 μM, "b" indicates activity of ≤ 1 μM, and "c" indicates activity of ≤ 5 μM.

3. Histone H4 acetylation in whole cells by immunoblots

[0903] T24 human bladder cancer cells growing in culture were incubated with HDAC inhibitors for 16 h. Histones were extracted from the cells after the culture period as described by M. Yoshida *et al.* (*J. Biol. Chem.* **265(28)**: 17174-17179 (1990)). 20 g of total histone protein was loaded onto SDS/PAGE and transferred to nitrocellulose membranes. Membranes were probed with polyclonal antibodies specific for acetylated histone H-4 (Upstate Biotech Inc.), followed by horse radish peroxidase conjugated secondary antibodies (Sigma). Enhanced Chemiluminescence (ECL) (Amersham) detection was performed using Kodak films (Eastman Kodak). Acetylated H-4 signal was quantified by densitometry. Representative data are presented in Table 14. Data are presented as the ratio of the concentration effective for reducing the acetylated H-4 signal by 50% (EC_{50}) using the indicated compound of the invention to a control compound, MS-275. If the indicated ratio is 1, then the compound of the invention is as effective as the MS-275 control compound. If the ratio is less than 1, then the compound of the invention is more effective than the MS-275 control compound. Further information regarding the MS-275 compound can be found in Suzuki et al., *J. Med. Chem.* 1999, pp. 3001-3003.

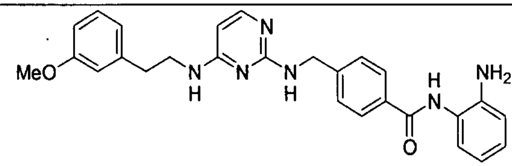
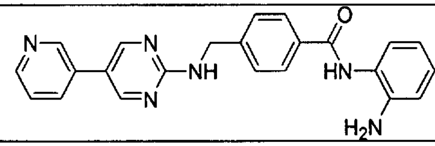
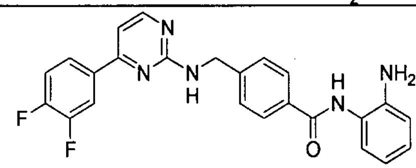
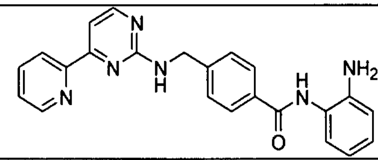
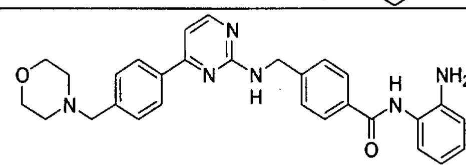
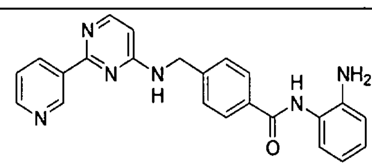


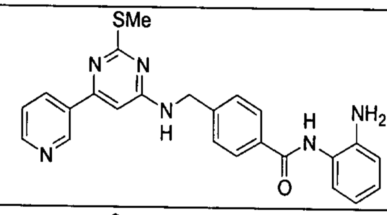
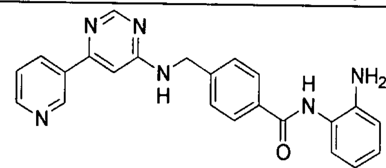
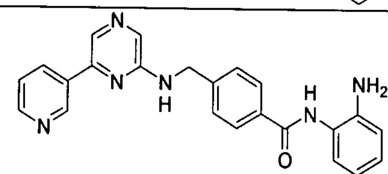
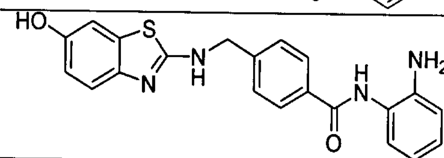
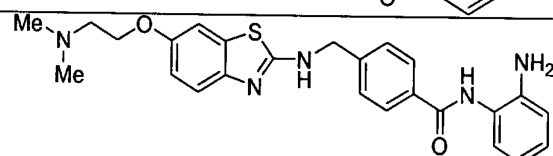
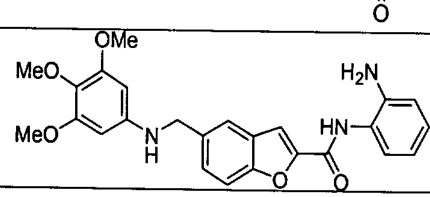
MS-275

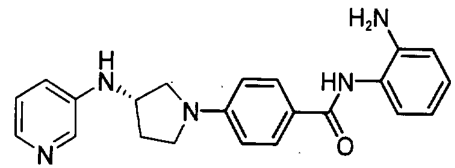
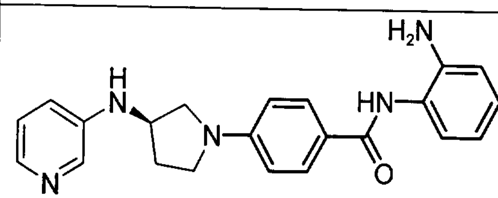
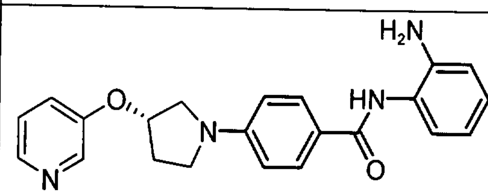
4. Histone H3 acetylation assay

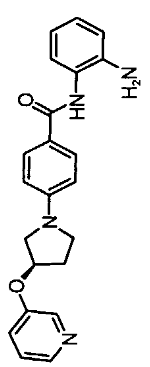
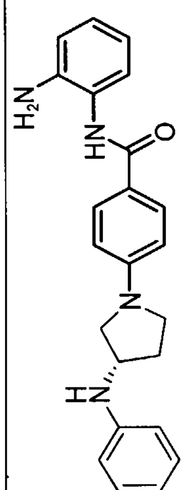
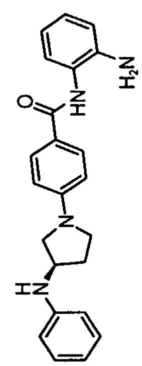
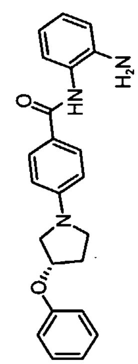
[0904] T24 human bladder cancer cells growing in culture are incubated with HDAC inhibitors for 16 h. Cell viability is determined by adding 10 µl Alamar Blue (BioSource, DAL1100). Cells are washed once with PBS and fixed with methanol precooled to -20 °C for 10 min. The cells are then washed twice in PBS. The fixed cells are blocked with 50 µl of PBS + 0.1% Triton X-100. Cells are probed with rabbit-anti-acetyl-H3 (Upstate #06-599) as the primary antibody and then with goat-anti-rabbit-HRP (Sigma #A-0545) as the secondary antibody. Fluorescence is read by fluorometer at Ex:550, Em:610, Cutoff:590 (Auto PMT, 15 reads/well) after addition of Amplex-Red. Fluorescence signal is normalized against cell viability derived from Alamar Blue. Data is presented in Table 14 as EC_{50}. Maximum acetylation signal of MS-275 (fluorescence unit) is measured as E_{max}. The concentration of compound which gives 50% of E_{max} is EC_{50}. In Table 14, "x" indicates activity of ≤ 1 µM, "y" indicates activity of ≤ 10 µM, and "z" indicates activity of ≤ 20 µM.

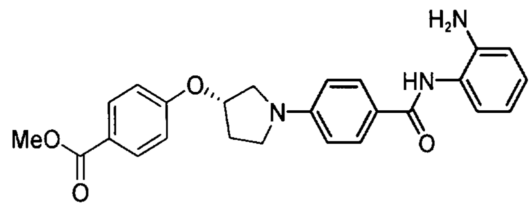
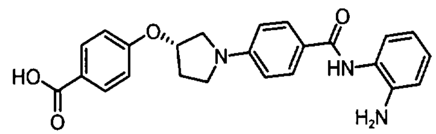
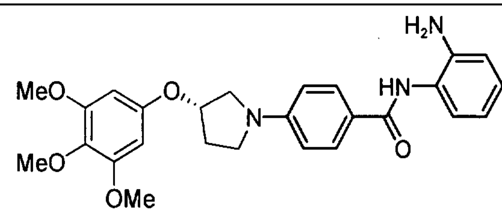
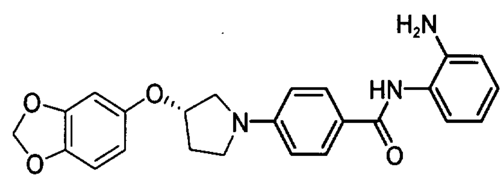
Table 14: ***In vitro*** **profile of selected HDAC inhibitors.**

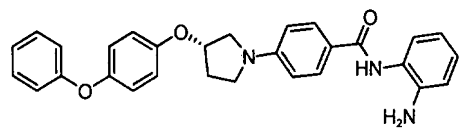
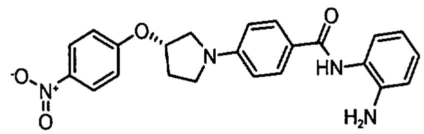
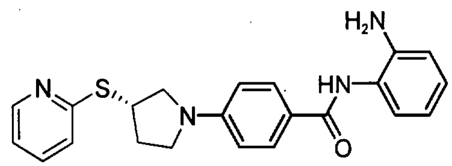
Example	Compd	Structure	HDAC-1 IC_{50} (μM)	MTT HCT116 IC_{50} (μM)	H4-Ac T24 EC vs. MS-275
4	**10c**		**c**	**b**	**v**
16	**13e**		**c**	**b**	**v**
20	**16d**		**b**	**b**	**v**
30	**26b**		**c**	**a**	**v**
42	**44**		**c**	**a**	**v**
43	**47**		**c**	**b**	**u**

Example	Compd	Structure	HDAC-1 IC_{50} (μM)	MTT HCT116 IC_{50} (μM)	H4-Ac T24 EC vs. MS-275
48	61a		c	a	v
49	61b		c	a	u
51	63		c	b	v
72	134		c	b	u
76	138		c	a	u
173	308		c	b	w

Example	Comp	Structure	HDAC1 IC50 uM	MTT HCT116 IC50 (mM)	H3 Ac t24 (uM)
193	361		a	b	y
194	366		b	c	z
195	367		b	b	y

196	368		b	b	
197	369		b	b	x
198	370		c	c	
199	371		b	b	

200	372		a	b	
201	373		b	d	
202	374		a	b	x
203	375		a	d	x

204	376		c	c	
205	377		b	b	
206	378		b	b	y

Assay Example 2

Antineoplastic Effects of Histone Deacetylase Inhibitors on Human Tumor Xenografts *In Vivo*

[0905] Eight to ten week old female BCD1 mice (Taconic Labs, Great Barrington, NY) were injected subcutaneously in the flank area with 2 x 10^6 preconditioned HCT116 human colorectal carcinoma cells, SW48 colon cancer cells, and A549 lung cancer cells. Preconditioning of these cells was done by a minimum of three consecutive tumor transplantations in the same strain of nude mice. Subsequently, tumor fragments of approximately 30 mgs were excised and implanted subcutaneously in mice, in the left flank area, under Forene anesthesia (Abbott Labs, Geneva, Switzerland). When the tumors reached a mean volume of 100 mm^3, the mice were treated intraperitoneally by daily injection, with a solution of the histone deacetylase inhibitor in DMSO, at a starting dose of 10 mg/kg. The optimal dose of the HDAC inhibitor was established by dose response experiments according to standard protocols. Tumor volume was calculated every second day post infusion according to standard methods (*e.g.*, Meyer *et al.*, *Int. J. Cancer* **43**: 851-856 (1989)). Treatment with the HDAC inhibitors according to the invention caused a significant reduction in tumor weight and volume relative to controls treated with vehicle only (*i.e.*, no HDAC inhibitor).

Assay Example 3

Combined Antineoplastic Effect of Histone Deacetylase Inhibitors and Histone Deacetylase Antisense Oligonucleotides on Tumor Cells *In Vivo*

[0906] The purpose of this example is to illustrate the ability of the combined use of a histone deacetylase inhibitor of the invention and a histone deacetylase antisense oligonucleotide to enhance inhibition of tumor growth in a mammal. Preferably, the antisense oligonucleotide and the HDAC inhibitor inhibit the expression and activity of the same histone deacetylase.

[0907] Mice bearing implanted HCT116 tumors (mean volume 100 mm^3) are treated daily with saline preparations containing from about 0.1 mg to about 30 mg per kg body weight of histone deacetylase antisense oligonucleotide. A second group of mice is treated daily with pharmaceutically acceptable preparations containing from about 0.01 mg to about 5 mg per kg body weight of HDAC inhibitor.

[0908] Some mice receive both the antisense oligonucleotide and the HDAC inhibitor. Of these mice, one group may receive the antisense oligonucleotide and the HDAC inhibitor simultaneously intravenously via the tail vein. Another group may receive the antisense oligonucleotide via the tail vein, and the HDAC inhibitor subcutaneously. Yet another group may

receive both the antisense oligonucleotide and the HDAC inhibitor subcutaneously. Control groups of mice are similarly established which receive no treatment (*e.g.*, saline only), a mismatch antisense oligonucleotide only, a control compound that does not inhibit histone deacetylase activity, and a mismatch antisense oligonucleotide with a control compound.

[0909] Tumor volume is measured with calipers. Treatment with the antisense oligonucleotide plus the histone deacetylase protein inhibitors according to the invention causes a significant reduction in tumor weight and volume relative to controls.

Table 15. % Inhibition (relative to vehicle control

Compound	Example	Dose mg/kg	Route	No. of animals entered	HCT116	SW48	A549
10a	2	30	ip	6	16.1	23.0	-
26b	30	40	ip	6	-	75.1	74.4
26c	32	30	ip	6	88.0	89.5	-
29a	34	30	ip	6	-	70.2	31.8
31b	37	30	ip	6	39.4	47.8	-
34a	39	30	ip	6	-	25.5	67.1
58b	47	30	ip	6	29.4	34.6	-
138	76	30	ip	6	79.8	-	83.7
158	82	30	ip	6	-	43.2	42.6
194	93	30	ip	6	54.5	23.1	-
212f	104	30	ip	6	65.7	32.7	-
212h	106	30	ip	6	-	44.0	54.4
252	133	30	ip	6	70.6	25.9	-
298	161	30	ip	6	63.9	53.4	-

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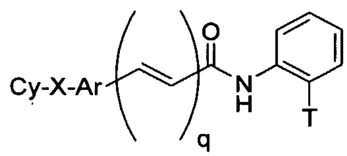
We claim:

1. A compound of formula (1):



(1)

or a pharmaceutically acceptable salt thereof, wherein

Cy is aryl, heteroaryl, cycloalkyl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

X is selected from the group consisting of a chemical bond, L, W-L, L-W, and L-W-L, wherein

W, at each occurrence, is S, O, C=O, or $N(R^9)$, where R^9 is selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and t-butoxycarbonyl; and

L, at each occurrence, is independently C_1-C_4 alkylene;

Ar is arylene or heteroarylene, each of which is optionally substituted;

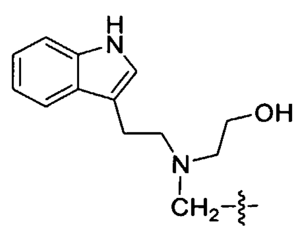
q is 0 or 1; and

T is NH_2 or OH,

provided that when Cy is naphthyl, X is $-CH_2-$, Ar is phenyl, and q is 0 or 1, T is not OH.

2. A compound according to claim 1 wherein q is 1, and T is NH_2.

3. A compound according to claim 2 wherein Ar is phenylene, and Cy-X- is



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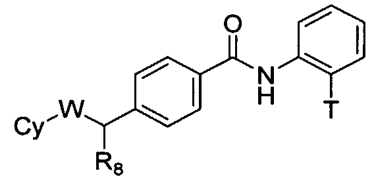
4. A compound according to claim 1 wherein q is 0.

5. A compound according to claim 4, of the formula (1a)



(1a)

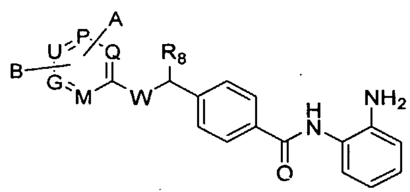
wherein

W is S, O, or N(R_9), wherein R_9 is hydrogen or alkyl; and

R_8 is H or C_1-C_4 alkyl.

6. A compound according to claim 5 wherein wherein Cy is selected from phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiazolyl, benzothiazolyl, benzoimidazolyl, and benzotriazolyl, each of which is optionally substituted.

7. A compound according to claim 5 of the formula 1a-1:



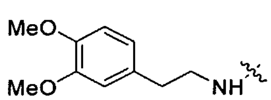
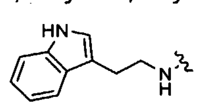
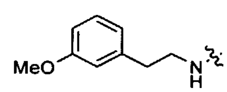
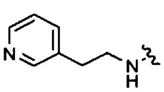
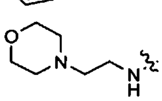
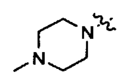
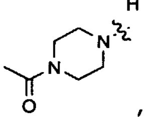
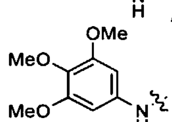
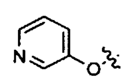
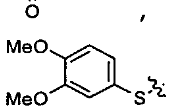
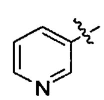
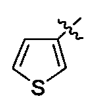
1a-1

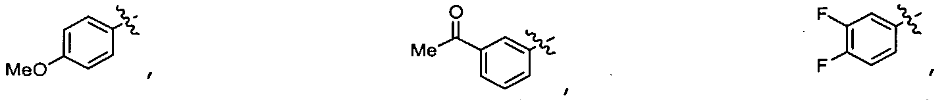
wherein W is NH or S;

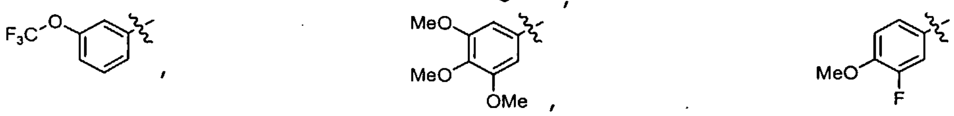
P, Q, M, G and U are independently CH or N, provided that no more than two of P, Q, M, G and U are N and in the ring containing P, Q, M, G, and U, an annular S or O is not adjacent to another annular S or O;

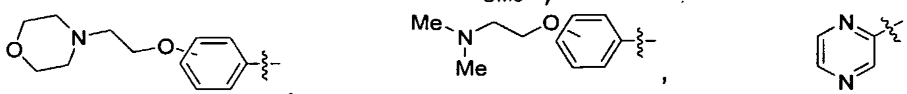
R_8 is H or C_1-C_4 alkyl; and

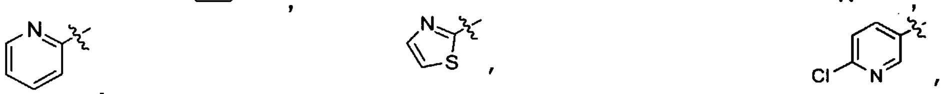
groups A and B are the same or different and are independently selected from H, halogen, C_1-C_4 alkyl, optionally substituted alkoxy including aminoalkoxy, haloalkoxy and heteroarylalkoxy, alkoxyalkyl, haloalkyl, amino, nitro, alkylthio, acylamino, carbamoyl,

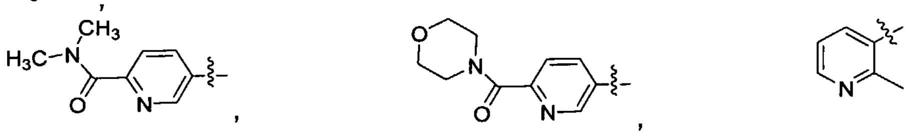
,
,
,
,
,
,
,
,
,
,
,
,

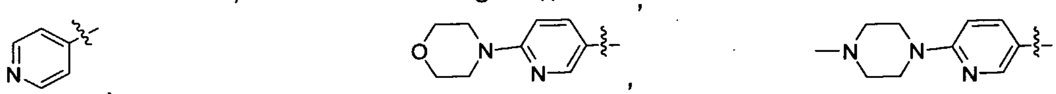


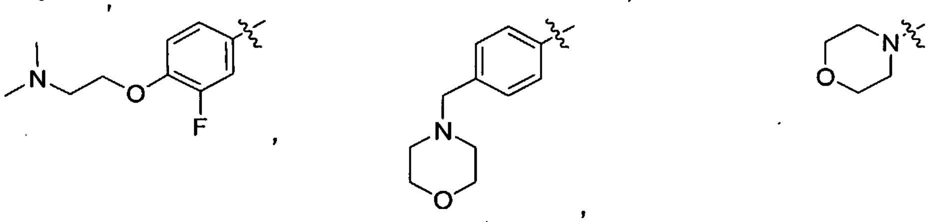


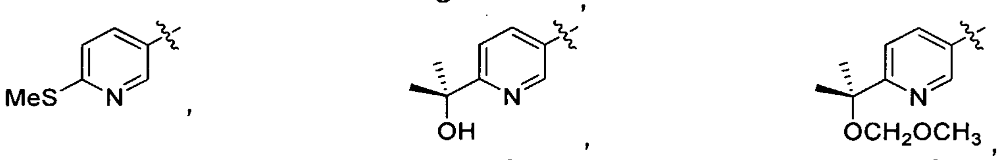


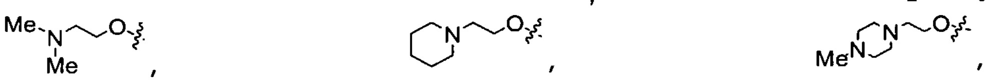


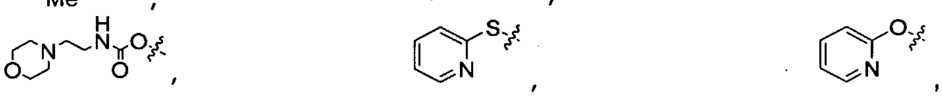


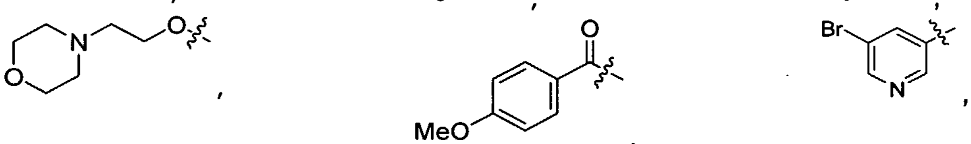


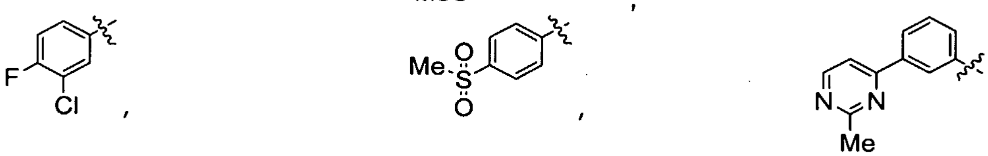


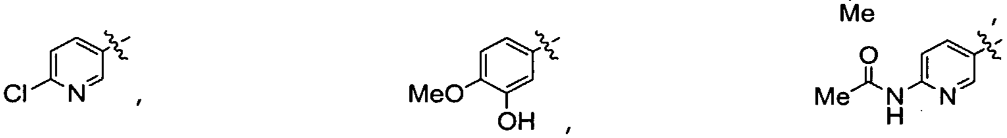


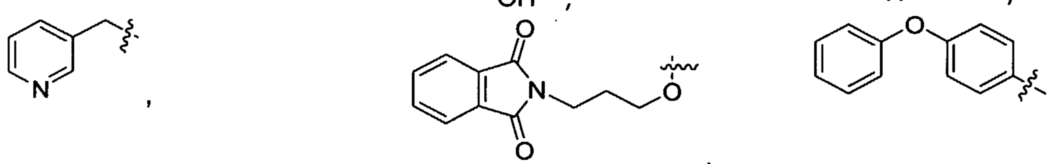


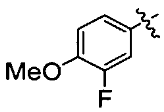
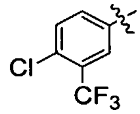
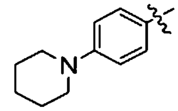
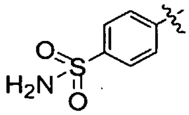
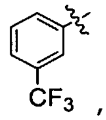
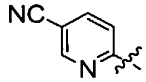
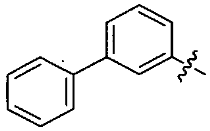
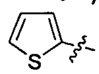
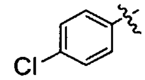
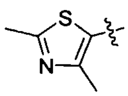
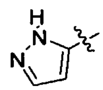
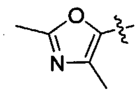
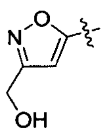
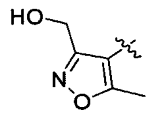
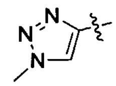
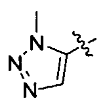
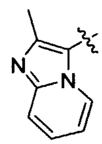
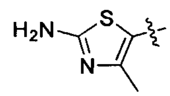
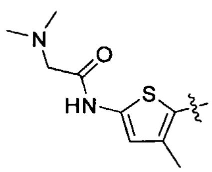
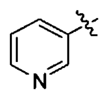
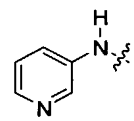
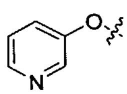
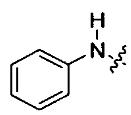
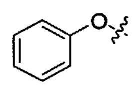
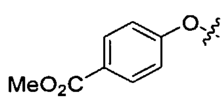
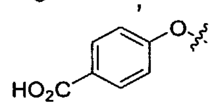
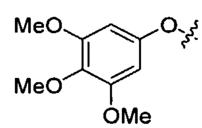
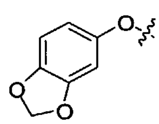
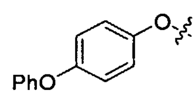
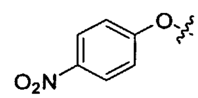
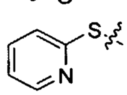
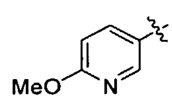
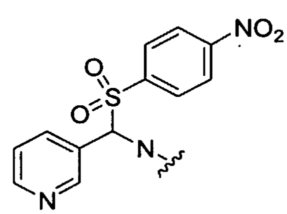
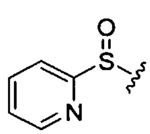
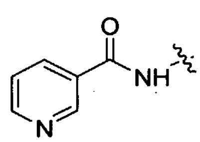




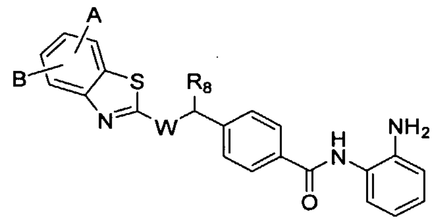






,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
.
,
, and
.

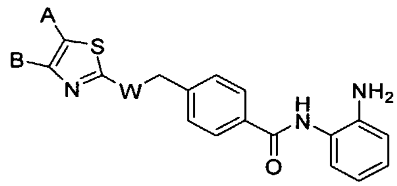
8. A compound according to claim 5 of the formula 1a-2:



1a-2

wherein W is S or NH; R_8 is H or C_1-C_4 alkyl; and A and B are as defined in claim 7.

9. A compound according to claim 5 of the formula 1a-3:

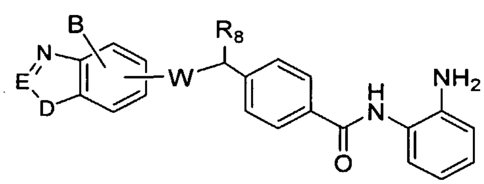


1a-3

and pharmaceutically acceptable salts thereof, wherein W is S or NH, and A and B are as defined in claim 7.

10. A compound according to claim 9 wherein W is NH.

11. A compound according to claim 5 of the formula 1a-4:

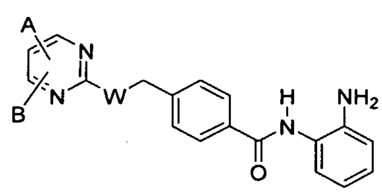


1a-4

wherein W is S or NH; D is N-R_{10} or S, E is N or C-A; R_8 and R_{10} are independently H or C_1-C_4 alkyl; and A and B are as defined in claim 7.

12. A compound according to claim 11 wherein W is NH.

13. A compound according to claim 7 of the formula 1a-5:

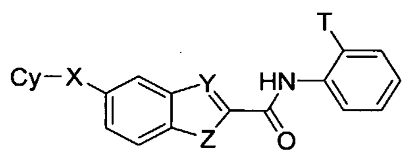


1a-5.

14. A compound according to claim 13 wherein W is NH.

15. A compound according to claim 5 wherein W is NH and Cy is quinoxalinyl, phthalimidyl, or benzodioxolyl, each of which is optionally substituted with A and/or B, wherein A and B are as defined below.

16. A compound according to claim 1, of the formula (1b):



(1b)

wherein

X is L, W-L, or L-W, wherein

W, at each occurrence, is S, O, or NH; and

L is $-CH_2-$;

Y is N or CH; and

Z is O, S, NH or CH_2.

17. A compound according to claim 16 wherein T is NH_2.

18. A compound according to claim 16 wherein X is $-S-CH_2-$, $-NH-CH_2-$ or $-CH_2-NH-$.

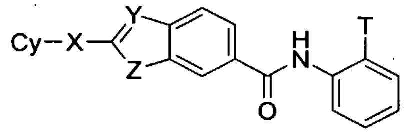
19. A compound according to claim 16 wherein Cy is aryl or heteroaryl, each of which is optionally substituted.

20. A compound according to claim 16 wherein Cy is phenyl, pyridyl, pyrimidinyl, or benzothiazolyl, each of which is optionally substituted.

21. A compound according to claim 16 wherein Cy is substituted with A and/or B, wherein A and B are as defined in claim 7.

22. A compound according to claim 16 wherein Cy is optionally substituted with one, two or three groups independently selected from alkoxy, acyl, morpholino, and phenyl optionally substituted with alkoxy.

23. A compound according to claim 1 of the formula (1c):



(1c)

X is L, W-L, or L-W, wherein

W, at each occurrence, is S, O, or NH; and

L is $-CH_2-$;

Y is N or CH; and

Z is O, S, NH or CH_2.

24. A compound according to claim 23 wherein T is NH_2.

25. A compound according to claim 23 wherein X is $-S-CH_2-$, $-NH-CH_2-$ or $-CH_2-NH-$.

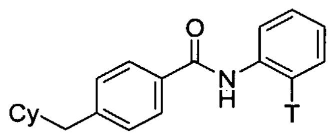
26. A compound according to claim 23 wherein Cy is aryl or heteroaryl, each of which is optionally substituted.

27. A compound according to claim 23 wherein Cy is phenyl, pyridyl, pyrimidinyl, or benzothiazolyl, each of which is optionally substituted.

28. A compound according to claim 23 wherein Cy is substituted with A and/or B, wherein A and B are as defined in claim 7.

29. A compound according to claim 23 wherein Cy is optionally substituted with one two or three groups independently selected from alkoxy, haloalkoxy, acyl, morpholino, or phenyl optionally substituted with alkoxy.

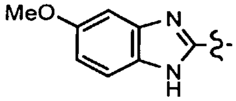
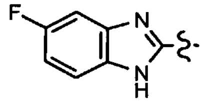
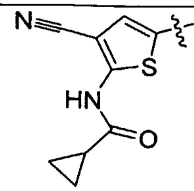
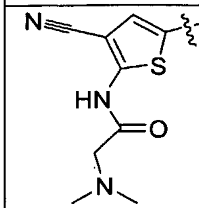
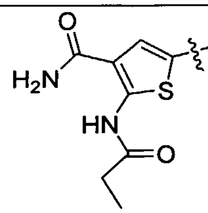
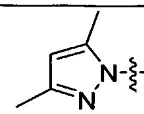
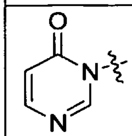
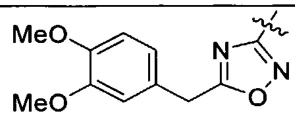
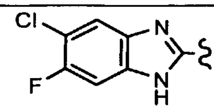
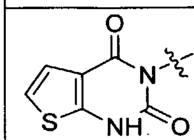
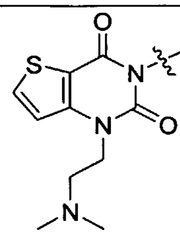
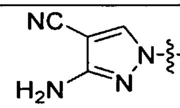
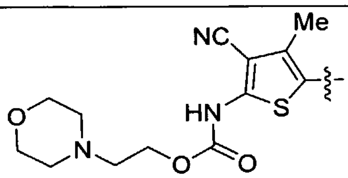
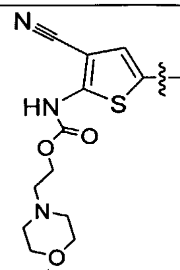
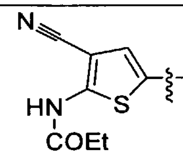
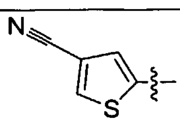
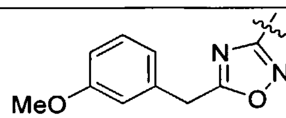
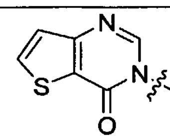
30. A compound according to claim 1, of the formula (1d):



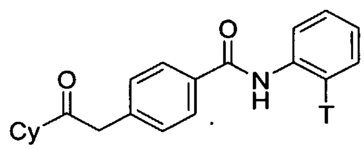
(1d).

31. A compound according to claim 30 wherein T is NH_2.

32. A compound according to claim 30 wherein Cy is:

		
		
		
		
		
	,  or	 .

33. A compound according to claim 1, of the formula (1e):



(1e).

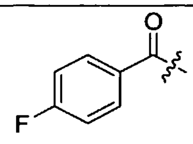
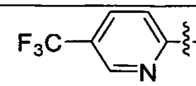
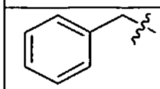
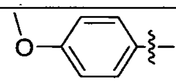
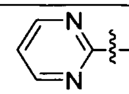
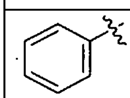
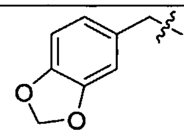
34. A compound according to claim 33 wherein T is NH_2.

35. A compound according to claim 33 wherein Cy is heterocyclyl or heteroaryl, each of

which is optionally substituted, and each of which contains at least one nitrogen atom as part of the ring.

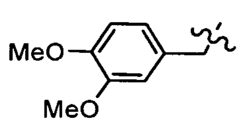
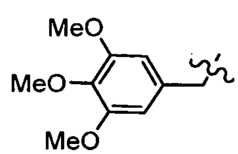
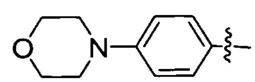
36. A compound according to claim 34 wherein Cy is optionally substituted with one or two substituents independently selected from A and B, wherein A and B are as defined in claim 7.

37. A compound according to claim 33 wherein Cy is optionally substituted with one or two substituents independently selected from:

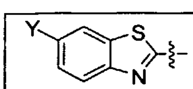
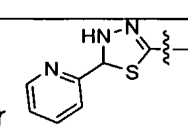
-CN,	 ,	 ,
 ,	 ,	 ,
 , and	 ..	

38. A compound according to claim 4 wherein Ar is phenylene, indolyl or indolinyl, each of which is optionally substituted, and X is absent, CH_2, $-O-CH_2-$, $-S-CH_2-$, $-S-C(CH_3)(H)-$, or $-N(R_9)-CH_2-$.

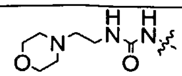
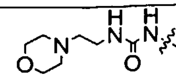
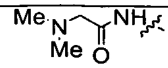
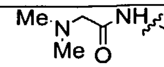
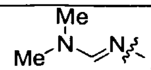
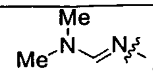
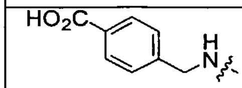
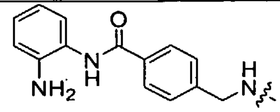
39. A compound according to claim 38 wherein Ar is an indolyl or indolinyl group, X is CH_2 or $-N(R_9)-CH_2-$, and Cy is:

 ,  or  .

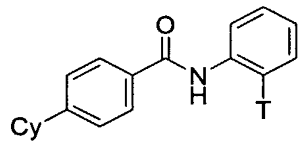
40. A compound according to claim 38 wherein Ar is phenylene, X is $-S-CH_2-$, or $-S-C(CH_3)(H)-$, and Cy is:

 ,	or  ,

wherein Y is selected from:

 ,	 ,
 ,	 ,
 ,	 ,
 , and	 .

41. A compound according to claim 1, of the formula (1f):

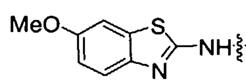


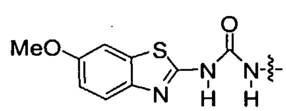
(1f).

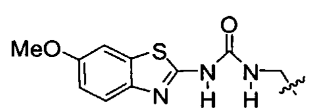
42. A compound according to claim 41 wherein Cy is heterocyclyl or heteroaryl, each of which is optionally substituted, and each of which contains at least one nitrogen atom as part of the ring.

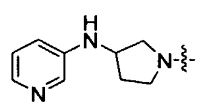
43. A compound according to claim 42 wherein Cy is bound to the phenyl through a nitrogen atom.

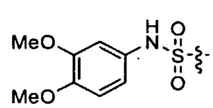
44. A compound according to claim 41 wherein Cy is:

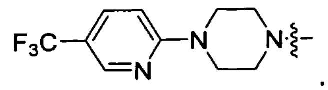
 ,

 ,

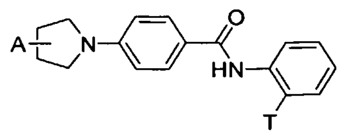
 .

 ,

 , or



45. A compound according to claim 41 of the formula (1f-1):

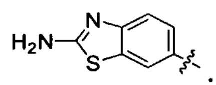


(1f-1)

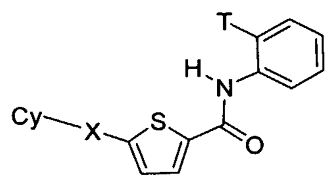
wherein A is as defined in claim 7.

46. A compound according to claim 45 wherein T is NH_2.

47. A compound according to claim 38 wherein Ar is phenylene, X is $-O-CH_2-$, and Cy is:



48. A compound according to claim 1 of the formula (1g):



(1g)

wherein

Cy is aryl, or heteroaryl, cycloalkyl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

X is L, W-L, or L-W, wherein

W, at each occurrence, is S, O, or NH; and

L is $-CH_2-$;

T is NH_2 or OH.

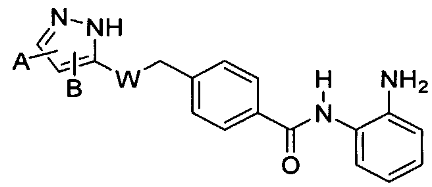
49. A compound according to claim 48 wherein Cy is optionally substituted heteroaryl.

50. A compound according to claim 48 wherein Cy is optionally substituted pyrimidinyl.

51. A compound according to claim 48 wherein X is $-NH-CH_2-$.

52. A compound according to claim 48 wherein T is NH_2.

53. A compound according to claim 1of the formula (1h):



(1h)

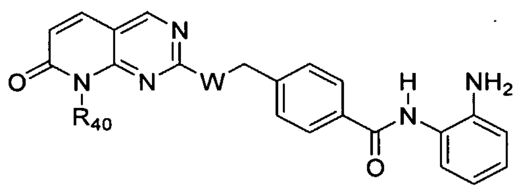
where W is S, O, or NH and A and B are as defined in claim 7.

54. A compound according to claim 53 wherein W is NH.

55. A compound according to claim 53 wherein A is optionally substituted pyridyl or optionally substituted phenyl.

56. A compound according to claim 53 wherein B is H or halo.

57. A compound according to claim 1 of the formula (1i):



(1i)

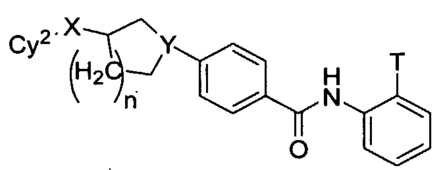
where W is S, O, or NH and R_{40} is H or C_1-C_6 alkyl.

58. A compound according to claim 57 wherein W is NH.

59. A compound according to claim 57 wherein R_{40} is H.

60. A compound according to claim 57 wherein R_{40} is methyl.

61. A compound of formula (2)



(2)

or a pharmaceutically acceptable salt thereof, wherein

Cy^2 is aryl or heteroaryl, each of which is optionally substituted and wherein each of aryl andheteroaryl is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

X is selected from the group consisting of: a covalent bond, C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(CO)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(NR^7)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl-(S)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(O)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(SO)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(SO_2)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(NH)-(CO)-C_0-C_4-hydrocarbyl, C_0-C_4-hydrocarbyl -(CO)-(NH)-C_0-C_4-hydrocarbyl, -NH-CO-NH-, -NH-CS-NH-, -O-CO-O-, -O-CS-O-, -NH-C(NH)-NH-, -$S(O)_2$-$N(R^7)$-, -$N(R^7)$-$S(O)_2$-, -NH-C(O)-O-, and -O-C(O)-NH-,

wherein R^7 is selected from the group consisting of hydrogen, C_1-C_5-alkyl, aryl, aralkyl, acyl, heterocyclyl, heteroaryl, SO_2-alkyl, SO_2-aryl, CO-alkyl, CO-aryl, CO-NH-alkyl, CO-NH-aryl, CO-O-alkyl and CO-O-aryl, each of which is optionally substituted,

n is 0 to 4,

Y is N or CH, and

T is NH_2 or OH.

62. A compound according to claim 61 having S stereochemistry.

63. A compound according to claim 61 having R stereochemistry.

64. A compound according to claim 1, selected from the group consisting of:

N-(2-Amino-phenyl)-4-[(6-hydroxy-benzothiazol-2-ylamino)-methyl]-benzamide;

N-(2-Amino-phenyl)-4-[(4-pyridin-4-yl-pyrimidin-2-ylamino)-methyl]-benzamide;

N-(2-Amino-phenyl)-4-[3-(pyridin-3-ylamino)-pyrrolidin-1-yl]-benzamide;

N-(2-Amino-phenyl)-4-[(2-methylsulfanyl-6-pyridin-3-yl-pyrimidin-4-ylamino)-methyl]-benzamide;

N-(2-aminophenyl)-4-((4-(1-methyl-1H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide;

(S)-*N*-(2-Aminophenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide;

(R)-*N*-(2-aminophenyl)-4-(3-(pyridin-3-ylamino)pyrrolidin-1-yl)benzamide;

(S)-N-(2-Aminophenyl)-4-(3-(pyridin-3-yloxy)pyrrolidin-1-yl)benzamide

(R)-N-(2-Aminophenyl)-4-(3-(pyridin-3-yloxy)pyrrolidin-1-yl)benzamide;

N-(2-aminophenyl)-4-((4-(3-methyl-3H-1,2,3-triazol-4-yl)pyrimidin-2-ylamino)methyl)benzamide;

N-(2-Amino-phenyl)-4-{[4-(2,4-dimethyl-oxazol-5-yl)-pyrimidin-2-ylamino]-methyl}-benzamide;

(S)-N-(1-(4-(2-Aminophenyl carbamoyl)phenyl)pyrrolidin-3-yl)nicotinamide;

(S)-N-(2-Aminophenyl)-4-(3-(pyridin-2-ylthio)pyrrolidin-1-yl)benzamide;

N-(2-Aminophenyl)-4-((S)-3-((S)-pyridin-2-ylsulfinyl)pyrrolidin-1-yl)benzamide;

and N-(2-Amino-phenyl)-4-[1-(2-dimethylamino-ethyl)-2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl]-benzamide.

65. A composition comprising a mixture of enantiomers of compounds of claim 61.

66. The composition of claim 65 wherein the mixture is racemic.

67. The composition of claim 65 wherein the mixture is enantiomerically enriched.

68. A composition comprising one or more compounds according to any one of claims 1-64 and a pharmaceutically acceptable carrier.

69. A method of inhibiting histone deacetylase in a cell, the method comprising contacting a cell with one or more compounds according to any one of claims 1-64 or a composition comprising one or more compounds according to any one of claims 1-64 and a pharmaceutically acceptable carrier.

70. A method for treating a cell proliferative disease or condition in an animal, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of one or more compounds according to any one of claims 1-64 or a composition comprising one or more compounds according to any one of claims 1-64 and a pharmaceutically acceptable carrier.

71. A method according to claim 70 wherein the animal is a mammal.

72. A method according to claim 70 wherein the animal is a human.

73. A method according to claim 70 wherein the cell proliferative disease or condition is neoplastic cell proliferation.

74. A method of inhibiting histone deacetylase in a cell, the method comprising contacting a cell with a composition of any one of claims 65-67 or a composition of any one of claims 65-67 together with a pharmaceutically acceptable carrier.

75. A method for treating a cell proliferative disease or condition in an animal, the method comprising administering to an animal in need of such treatment a therapeutically effective amount of a composition according to any one of claims 65-67 or a composition of any one of claims 65-67 together with a pharmaceutically acceptable carrier..

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/000454

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7): C07D 495/04, A61K 31/505, A61K 31/455, A61K 31/5377, A61K 31/496, A61K 31/428, A61K 31/343, A61K 31/4439, A61K 31/40, A61K 31/36, C07D 471/04, C07D 413/12, C07D 413/10, C07D 403/04, C07D 401/04, C07D 209/14, C07D 277/68

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(7): C07D 495/04, A61K 31/505, A61K 31/455, A61K 31/5377, A61K 31/496, A61K 31/428, A61K 31/343, A61K 31/4439, A61K 31/40, A61K 31/36, C07D 471/04, C07D 413/12, C07D 413/10, C07D 403/04, C07D 401/04, C07D 209/14, C07D 277/68

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, STN, Delphion, Espacenet (Search terms: "HDAC", "histone", "deacetylase", "neoplastic", "proliferat*").

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/024448 A2 (DELORME ET AL.) 27 March 2003 (27-03-2003) entire document (cited in the application)	1-75
X	CA 2, 490, 579 A1 (BESTERMAN ET AL.) 15 January 2004 (15-01-2004) entire document	1, 2, 4-8, 13-15, 38, 39 and 68-73
X	CA 2, 480, 356 A1 (STOKES ET AL.) 23 October 2003 (23-10-2003) entire document	1, 4, 38, 41-43, 45, 46 and 61-75
X	CA 2, 484, 065 A1 (STOKES ET AL.) 13 November 2003 (13-11-2003) entire document	1, 4, 64 and 68-73
X	JP 11269146 A2 (SUZUKI ET AL.) 05 October 1999 (05-10-1999) entire document	1 and 4

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2005 (15-07-2005)	11 August 2005 (11-08-2005)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer
Cara Weir (819) 934-2322

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 69-75
because they relate to subject matter not required to be searched by this Authority, namely :

   Although claims 69-75 are directed to a method of medical treatment of the human or animal body, the search has been carried out based on the alleged effects of the compounds and compositions thereof.

2. [ ] Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/000454

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2004/069133 A2 (FERTIG ET AL.) 19 August 2004 (19-08-2004) entire document	1, 16, 17, 19, 20 and 68-73
X, P	WO 2004/069823 A1 (DELORME ET AL.) 19 August 2004 (19-08-2004) entire document	1, 4-7, 13, 14 and 68-73

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA2005/000454

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO03024448	27-03-2003	BR0212510 A	24-08-2004
		CA2465978 A1	27-03-2003
		CN1578663 A	09-02-2005
		EP1429765 A2	23-06-2004
		JP2005508905T T	07-04-2005
		US6897220 B2	24-05-2005
		US2004106599 A1	03-06-2004
		WO2004069823 A1	19-08-2004
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		WO2004005513 A2	15-01-2004
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		BR0308875 A	04-01-2005
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		BR0309553 A	09-02-2005
		EP1501508 A1	02-02-2005
		GB0209715D D0	05-06-2002
		WO03092686 A1	13-11-2003
JP 11269146	05-10-1999	None	
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WO2004069823	19-08-2004	BR0212510 A	24-08-2004
		CA2465978 A1	27-03-2003
		CN1578663 A	09-02-2005
		EP1429765 A2	23-06-2004
		JP2005508905T T	07-04-2005
		US6897220 B2	24-05-2005
		US2004106599 A1	03-06-2004
		WO03024448 A2	27-03-2003